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TRIBBLE, a Molecular Modelling System for the Public Domain

© Lee W. Herman, M.Sc.

A thesis submitted to the Faculty of

Graduate Studies in partial fulfilment

of the requirements for the degree of

Doctor of Philosophy

Department of Chemistry

Carleton University

March 1987.

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The undersigned hereby recommend to the Faculty of Graduate Studies the acceptance of this thesis submitted by Lee Whitney Herman, M.Sc., in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

In the first chapter, the redesigning of TRIBBLE, a molecular modelling software package obtained from DuPont de Nemours, Inc., is described. Those principles of theoretical chemistry pertaining to contemporary software are introduced, and the practical limitations of the original package elaborated. Improvements to the system, and examples of applications to drug design and the elucidation of reaction mechanisms, are described. A simulated TRIBBLE user session, as well as studies into the attempted synthesis of a cyclobenzazaundecine derivative with potential anticancer properties, are included as appendices.

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I could not have accomplished this work without the constant, unconditional support of my parents and family.

And finally I thank Carleton University for its financial assistance and its warm, sheltered environment.

**TRIBBLE, a Molecular Modelling System
for the Public Domain**

Foreword

TRIBBLE was announced in the May 1987 issue of the QCPE Bulletin as QCPE 529.

The name "TRIBBLE" referred to a small furry alien creature in the TV science fiction series "Star Trek". The original creator of our computer modelling system, Dave Pensak, named his dog in honour of these friendly beasts and, subsequently, the software system after his dog.

Due to possible copyright violations, the name of the system, which has been TRIBBLE to this day, will be changed to TRIBL.

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Introduction

History

Since the beginning of recorded history man has used his environment as a source of medicines. As early as 2735 B.C. the scholar-emperor Shen Nung observed the stimulant effect of the drug mā huang, later found to contain ephedrine¹. The ipecacuanha root was used in Brazil and the far east to treat dysentery and diarrhea; its active component, emetine, is still used to combat amebiasis.

Ancient medicine was not always so rigorously scientific. Galenus (A.D. 131-200) combined the Greek concept of four humors (heat, cold, moisture, and dryness) with metallurgical concepts; he investigated natural materials now believed to have useful therapeutic effects (viper venom, opium), as well as some whose effects are less benign (cadmium oxide). Paracelsus (A.D. 1493-1541) had a similar peculiar belief in the broad action of antimony and its salts.

Later discoveries, which had profound effects on civilization, included the introduction of anesthetics such as nitrous oxide (Davy), ether (Long, 1842), and chloroform (Simpson, 1843). Pure compounds isolated and popularized in the nineteenth century included morphine (Sertuner, 1806), atropine (Mein, Beiger, and Hesse, 1833); synthetic materials included salicylic acid (Kolbe), antipyrine (Knorr), and aspirin (Dreser, 1889).

It is only in the last one hundred years that the methodical investigation and development of derivatives of natural products has taken place. Heroin, or O-acetyl morphine, was hailed as a potent, non-addictive (!) alternative to natural morphine. Although a much abused substance, it still has a use in the treatment of pain for terminal cancer victims. A dramatically more successful example of early drug design is ASA, originally synthesized from oil of wintergreen. The most widely consumed synthetic drug in the world, ASA is still the agent of choice in the treatment of headache, and the pain associated with arthritis.

The previous examples, aspirin and heroin, illustrate the variation of a natural product, available easily from the natural source, and derivatized using very simple chemistry. Later, as methods for isolation and structure elucidation became more sophisticated (largely through the improvement of spectroscopic

and chromatographic techniques) and the arsenal of synthetic techniques grew, both the number of natural starting materials and the possibilities for structural manipulation increased; with these, of course, grew the number of synthetic compounds with potential for use as a drug. At this point the problem arose that without a systematic way to correlate the change in structure of a compound to its biological activity the number of guesses one had to make to produce a significantly more active compound became very great. Researchers often would synthesize a hundred or more derivatives of a "lead" molecule. The changes made were often trivial (eg. methyl, ethyl, or propyl ester of a starting acid), since they were simple to implement. Changes in the carbon skeleton, or functionalization at remote, non-activated sites were more difficult, but generally caused larger variation in activity. Using this approach, many man-years of research would often lead to compounds of only marginally greater activity or lesser toxicity.

The concept of the "structure-activity relationship" (SAR) grew out of the need to develop a strategy for rational drug design, and to lay the foundation for the elucidation of the mechanism of action for a given compound. Retrospective analysis of drug activity for a large series of compounds gave gross generalizations for structural requirements for activity. For instance, if

Receptor Mapping and the Pharmacophore

The activity of the majority of bioactive compounds is now accepted to be due to the interaction of a compound with its target receptor.

The drug-receptor interaction has been hypothesized to occur in up to three stages⁶⁻⁸. Briefly, this was determined by theoretically examining the interaction energy, conformations, and electron distributions of models of drugs and receptors as a function of relative distance and orientation. The drugs were benzene, simple quaternary ammonium compounds, methanol, aniline, and ethyl benzene, and the receptors were simply benzene, acetamide, acetate ion, and *n*-propylguanidinium ion. First, there is a long range recognition between the drug and receptor, without any perturbation of the drug. Thus, the recognition depends on the preferred conformation of that drug. After this point, the drug approaches the receptor, during which time there is perturbation of both the drug and the receptor. At the equilibrium distance, a stable drug-receptor complex is formed; the drug may exist in a relatively high energy conformation or electronic state. Finally, the complex undergoes a conformational change, driven by an increase in entropy, which causes the biological stimulus.

Kinetic studies on the interaction of the acetylcholine receptor and some agonists and antagonists suggest a two-step reaction, namely the formation of the drug-receptor complex followed by conformational change. Both stages occurred only in the presence of the agonists. Indeed, this defines the agonist. An antagonist binds to the receptor, competing with other molecules for a site, but does not evoke a conformational change and the accompanying biological response (unless, of course, the response is due to the lack of receptor innervation).

A pharmacophore may now be defined as some functional arrangement of elements (be they atoms or their electronic fields) which fulfills the spatial requirements of a receptor at each level of interaction. These pharmacophores have been labelled recognition, binding or affinity, and intrinsic pharmacophores, respectively.

Two strategies emerge when attempting to determine the pharmacophores for a desired drug effect. First, a group of agonists may be compared to each other; alternately, agonists may be compared to antagonists. The problem with the former is that not all the pharmacophores may be apparent; for example, the recognition and binding pharmacophores may be identified, but not the intrinsic one. This problem is alleviated

somewhat by the second method. Comparing agonists and antagonists suggests an analysis of the above situation, as the antagonists will possess the pharmacophores for recognition and binding, but not for perturbation of the receptor conformation. This assumes, however, that the agonist and antagonist bind to the same site. This is not the case with non-competitive antagonists, that compete with agonists by affecting enzyme conformation via binding to other sites.

The Static Model

The static pharmacophore is a representation of the interaction pharmacophore characterized by some spatial arrangement of atoms, usually heteroatoms and unsaturated systems, which is common to all or most of the drug molecules, and responsible for favorable recognition of the drug by the receptor. This approach is usually applied such that only one conformation of the drug is considered (often the low energy one). The static approach therefore requires that the low energy conformations be known for a group of active compounds (can be misleading), and that decisions be made as to the required heteroatoms (at worst, can be a wild guess). Since this approach

also does not address the question of the so-called intrinsic activity of a drug, it is quite limited.

The best example of a static approach is the classical Quantitative Structure Activity Relationship (QSAR) method pioneered by Hansch⁹⁻¹¹. In this approach, functional groups are assigned constants describing their steric, electronic, and solvent partitioning character. These constants are summed for each drug being investigated, and the resulting quantity, for each characteristic, are statistically related to drug activity. The art in this field comes not only in the determination of the values of the molecular descriptors, but in deciding what those descriptors should be! As of 1973, thirty-two different descriptors had been used in correlation studies.

At present, the QSAR approach has been extended to include descriptors not just related to functionality, but to a variety of molecular properties, such as interatomic distances, molecular volume and molecular surface area. Dihydrofolate reductase inhibition has been examined using this sort of approach¹². Hopfinger found that the quantities that correlated with the activity of a group of triazines were the steric overlap volume function (meaning that the active structures tended to have superimposable volumes), and the accessibility of a conformation with the two ring systems having a

torsional angle of 27 degrees (the latter represents an approach to be discussed later).

Examples of the static pharmacophore approach include work on the muscarinic receptor¹³, and the separation of the H1 and H2 histamine pharmacophores¹⁴.

The Electrostatic Potential Interaction Model

A major constraint of the static model is due to the fact that drug-receptor recognition is primarily an electrostatic phenomenon, and there may be a number of different spatial arrangements of atoms which lead to the same effective field; there may not be a unique static arrangement of atoms which can be defined as "optimum" for recognition to occur. This ambiguity is less likely if the electrostatic field is considered explicitly¹⁵.

With the advances in quantum mechanical calculations (which will be described in more detail later), it became possible to theoretically estimate the electrostatic potential around a given molecule. Early studies considered only two-dimensional slices of the field with the representation of various levels of

interaction in that plane¹⁶⁻¹⁹. A recent study using this approach presented evidence that the activity of tetrachlorodioxins was related to the decrease in electron density around the oxygens by the very electronegative halogens²⁰. As computing capabilities increased, it became possible to represent an electrostatic field as the three dimensional surface corresponding to a single energy level or, as color coded charge densities on the van der Waals surface. Weiner et. al. showed the hydrogen bonding and hydrophobic bonding sites of various enzymes, and demonstrated the electrostatic complementarity of these enzymes with their inhibitors²¹.

Molecular Interaction Calculations

To improve on the static model of drug-receptor interaction, Kiel and Holtje²² innovated the calculation of molecular interaction energies. Interaction energy is defined as the difference in energy between two isolated molecules and the same molecules at some interaction distance. To simulate a drug-receptor interaction, some small molecule, bearing functionality typical for an enzyme active amino acid residue, is allowed to interact with the test drugs; activity trends will parallel favourable interaction energy trends when the appropriate probe, site of interaction, and drug- probe distance are used. The

probe can be locked at some fixed orientation with respect to the drug²³, or several orientations may be evaluated²⁴.

This kind of active site model only considers one drug-receptor interaction at a time, which may reduce the complexity of the calculation to a large degree, but may also oversimplify the interaction to the point where it is not modelled correctly. This problem was demonstrated in one study²⁵ by using N-methylguanidine and benzene as surrogates for arginine and phenylalanine, as a model for the receptor responsible for the re-uptake of norepinephrine.

Molecular Superimposition

The evaluation of a recognition pharmacophore involves the comparison (whether it be electronic or spatial) of the low energy conformers of a group of drugs. The binding pharmacophore, on the other hand, may well be the result of a perturbed drug-receptor complex which is not described by the low energy conformer. To elucidate this pharmacophore, it is likely that a search of the accessible conformers, not just the lowest energy one, be made for the active drugs being used as the basis for the drug design. These conformers are

superimposed to reveal correspondences in atom position (again usually considering heteroatoms and pi systems). Plots of conformational energies, often with respect to selected dihedral angles, may also be compared.

The amount of energy above the low energy conformation that is considered "accessible" is crucial to the determination of superimposable structures. Generally, a value of 10-15 kcal has been allowed in the calculations^{26-28,28a,28b}, although lower energy tolerances have been used^{28c}.

Ghose and Crippen have developed a method for the quick evaluation of conformational energy and the elucidation of families of conformers, based solely on interatomic distances. To illustrate their technique they found a trend for certain torsion angles of a wide range of inhibitors²⁹ of dihydrofolate reductase, and identified a pharmacophore with 11 attractive sites and 5 repulsive ones.

Several techniques exist for the methodical evaluation of the extent of fit with respect to molecular conformation. Generally, a compound possessing high activity is chosen as a standard, and each of the test compounds is compared to it one by one. The simplest criterion for fit is the minimization of the distances between corresponding atoms of the two molecules³⁰. A similar

approach minimizes the total exposed molecular surface area of the overlapping molecules²⁷ or, analogously, maximizes the overlap volume³¹.

Molecular superimposition has been used for the determination of numerous pharmacophores. Green et al³² compared the structure of LSD with known H2 antagonists, and determined the superimposable moiety, assuming the correspondence of the LSD amide oxygen with various heteroatoms of the known antagonists (such as the cyano nitrogen of cimetidine). This moiety resembled an available compound, which later proved to be a potent H2 inhibitor.

Opiate analgesics have been extensively studied by superimposition techniques. Cheney and co-workers³³, after examining morphine using molecular mechanics, concluded that the skeleton was rather flexible. They were able to match four sites on morphine with corresponding ones on fentanyl and meperidine (two potent commercial analgesics) at an energy expenditure of less than 3 kcal/mole. Similarly, two groups studied the relation of enkephalins with morphine, assuming the existence of common active pharmacophores. Gorin and Marshall³⁴ matched the amino terminus and phenolic ring of ¹Tyr (of enkephalin) with the phenolic A ring and the nitrogen of morphine, and the meta and para positions of ⁴Phe with the C5 and C6

positions of morphine. Based on this model, they predicted the activity of synthetic enkephalin analogues based on their prediction of the binding conformation. These predictions later were shown to be correct³⁵. Loew et al³⁶ performed a similar study, and agreed on the importance of the tyramine residue for receptor binding, and identified a conformer of met-enkephalin which was superimposable on morphine at a cost of only 4 Kcal/mole above its low energy conformation.

The molecular superimposition approach may be enhanced by the calculation of other characteristics for the postulated binding conformation. For example, Cohen²⁷ displayed the electrostatic potentials, for a series of hypolipodemic agents, on space filling models, demonstrating their electronic as well as geometric similarities.

The Active Analogue Approach (AAA)

The active analogue approach, developed by Marshall and co-workers^{37,38} combines many of the characteristics of the previously mentioned ones, but introduces a dynamic factor. This difference is the

inclusion of consideration for all of the accessible conformers in an electronic and steric sense.

The AAA contains the following assumptions. First, the active compounds must contain a certain spatial arrangement of groups or heteroatoms. As in other approaches, this is known as the pharmacophore. The molecule must contain this pharmacophore, but it is not in itself sufficient for activity. Second, a definite and limited volume is available at the receptor site for binding; this is referred to as the "receptor excluded volume". The active compound must be able to fit within this volume; volume occupied by the receptor is referred to as "receptor essential volume". Obviously, the compound in question cannot simultaneously require this volume.

In order to constrain the complexity of the conformational calculations, several other assumptions are made. First, all of the the calculations of steric energy are done empirically using only Van der Waals interactions. Second, the conformational space that is searched in order to determine the receptor essential and excluded volumes is constrained within the range of interatomic distances of the atoms essential to the pharmacophore. This range must be common (and accessible) to all of the active compounds in question.

The following is a brief summary of the steps involved in an AAA analysis.

Initially, the pharmacophore must be evaluated. This is largely an intuitive process based on existing structure-activity relationships and biological data pointing to groups which "seem" to be essential for activity. As all future calculations are constrained by these initial assumptions, these guesses are the most crucial of all. Accessible conformations for the active compounds are determined, and the matrices describing the interatomic distances for the atoms of the pharmacophore are stored. The pharmacophore is then described by the sum of the accessible conformers projected onto an arbitrary 3-D frame of reference; the result is an orientation map.

The orientation map is then used to constrain the subsequent search of the conformational space of other test molecules. For each allowable conformation, using the pharmacophore as a frame of reference, a pseudo-electron density map (using Van der Waals functions) is constructed. The sum of these maps for all of the active compounds is called the receptor excluded volume; all later guesses at an active compound must fit within this volume. In an analogous calculation, inactive compounds are also evaluated. The volume produced by this calculation which does not lie within the receptor excluded

volume is known as the receptor essential volume, ie. this volume is occupied by the receptor itself. Any compound which occupies this volume within all of its accessible conformations will not fit the receptor.

Van der Waals functions were chosen as an appropriate probe for receptor specificity since they show a dependence on r^{-6} as opposed to electrostatic potentials which are dependant on the square of the interatomic distances. This dependance was proposed to be responsible for the high level of site discrimination.

Transition State Analogues

It was postulated almost forty years ago that inhibitors that resemble the transition state of an enzymatically catalyzed reaction will bind to that enzyme to a much greater extent than the substrate itself³⁹. This has led to a large number of studies of the design of transition state analogues as enzyme inhibitors^{40,41}. An example of the use of transition state analogue design was presented by Andrews⁴². In his study, he attempted to find a potent inhibitor of chorismate mutase, the enzyme found in bacteria which is responsible for the first step (a Claisen Rearrangement) in the biosynthesis of tyrosine and

phenylalanine. As this process does not occur in humans, the blocking of this step has the potential for the control of some bacteria, without side effects. First, it was necessary to model the transition state using MINDO/3. Two states, the chair and boat, were possible, and unfortunately were of similar energies (within 2 kcal). It was therefore necessary to synthesize rigid analogues mimicing both possible states. It was finally determined that adamantane-1-carboxylic acid, which resembled the chair transition state, was a good inhibitor.

Calculation of Molecular Energy

The ability to theoretically calculate energies associated with a given molecule is the basis of computer assisted molecular modelling and drug design. The methods used for these calculations may be broadly classed into three categories:

1. empirical (molecular mechanics)
2. semi-empirical (MO)

3. ab-initio (MO)

Molecular Mechanics

Principles

Molecular mechanics is a method which considers the nuclear position of the atoms in a molecule without an explicit consideration of the electronic properties, such as the molecular orbitals (MO's), of the system. The metaphor for this approach is therefore the mechanical molecular model; the conformation of a molecule is a function of the mechanical properties of the model. That is, the materials with which the model is constructed governs the outcome of the three-dimensional structure. If the bonds are made of steel, but held to the atoms with soft rubber, then the model will reflect a molecule with very stiff bond lengths and soft bending angles. Predictions made about systems using these materials will tend to give bonding distances which are very similar, but barriers to inversion (for cyclohexane, for example) which are very low.

For the successful calculation of conformation using molecular mechanics it is necessary to create a set of parameters which correctly describes the mechanical properties of a variety of systems. These parameters must be tailored to fit experimental data within the constraints of the particular description of the mechanical behaviour of molecular systems. In other words, the very basic quantities which are considered to describe the system are unique from author to author. These sets of descriptions are known as "force fields".

Force Fields

The concept of the force field was conceived in 1930 by Andrews⁴³, and applied to organic systems by Westheimer⁴⁴. In its simplest terms, a force field describes a molecule as a group of balls connected by springs. The molecule is considered to be in its low energy conformation when the sum of the forces on the springs is at a minimum. Notice that in this very crude type of molecular mechanics, known as the "hard sphere approach", the rotation around a single bond is determined by the contact of the atoms attached to the atoms of the single bond in question (ie. 1,4-interactions). Later force field

designers have tried to include various geometric descriptors which will cause the model to mimic experimentally derived energetic quantities more closely.

The most widely used force field is probably Allinger's MM2⁴⁵. According to this approach, the following basic relationships apply.

$$E_s = (k_s/2) (l - l_0)^2$$

$$E_\theta = (k_\theta/2) (\theta - \theta_0)^2$$

$$E_{vdw} = [-c_1(r^*/r)^6 + c_2 \exp(-c_3 r^*/r)]$$

$$E_\omega = [(V_1) (1 + \cos \omega) + (V_2/2) (1 + \cos 2\omega) + (V_3/3) (1 + \cos 3\omega)]$$

The first expression, based on Hooke's law, represents the stretching energy E_s , which is a parabolic function centered about the equilibrium distance l_0 and with the "steepness" of the curve modified by the stretching constant k_s . The bending energy, E_θ is analogous to the stretching energy. Bending constants are usually softer than stretching constants, and so a molecule will usually distort by changing a bonding angle rather than a bonding distance. Van der Waals energies, E_{vdw} , may be calculated if the quantities and r^* are estimated. These correspond to the hardness, and sum of the van der Waals radii, respectively (c_1 , c_2 , and c_3 are constants). Early force fields

required van der waals parameters for carbons and hydrogens which did not agree with known values for these quantities, in order to reproduce known rotational barriers for simple alkanes, such as butane (eg. hydrogens were too large and hard). To rectify this, the torsional parameter was introduced. This quantity explicitly adds steric energy as groups interact in a torsional sense; V_1 , V_2 , and V_3 are one, two, and three fold barriers respectively. Thus, double bonds have large V_2 parameters (to strongly induce planarity), and simple alkanes moderate positive V_3 quantities. The anomeric effect, for example, may be introduced by judicious selection of torsional parameters⁴⁶.

Other interactions considered in MM2 are the dipole interaction (which tends to correct for hydrogen bonding, although usually to too small a degree), and the stretch-bend interaction, describing the tendency for 1,3 oriented atoms to become more distant from the central atom as the angle defined by the three is decreased.

Applicability and Limitations

Molecular mechanics approaches to geometry have two very great advantages over MO calculations (which will be discussed later), namely increased speed and greater accuracy of conformational analysis. The length

of a calculation using a force field method generally increases with the square of the number of atoms in the molecule, whereas semi-empirical MO calculations increase with the cube, and ab initio MO calculations with the fourth power of the number of orbitals. This difference in speed is especially important during a geometry optimization, where hundreds of iterations may be necessary, or where the number of atoms may be very large (as in proteins or nucleic acids).

MM parameters are derived from experimental results, so calculated quantities tend naturally to be good approximations. This property, however, can also be a pitfall. In order to do an MM calculation, parameters must exist for the system being studied. If experimentally derived parameters from similar systems do not exist, then it is impossible to do a calculation; if they do exist, then it is still possible that they were derived poorly, as no straightforward method for translation exists. A force field is limited by the integrity of its parameters, and so a bad set of parameters will give bad results. This is particularly a problem where the user uses a "black box" approach to the calculation, as with casual use by a bench chemist. Furthermore, parameters obtained from one chemical system, under one set of conditions (eg. in

solution, or in the gas phase), or for one particular force field, may not be transferable.

MM approaches are also limited to molecular systems which do not deviate significantly from "normal" geometry. Consider the bonding distance between two atoms. Molecular mechanics predicts that the stretching force (ie. neglecting VDW effects) between the atoms increases exponentially as the two are drawn apart. In reality, the force function is Gaussian, and tails off as the interatomic distance becomes great. This and other factors limit somewhat the utility of MM to conformational analysis, and usually excludes the study of reaction dynamics.

Semi-Empirical Methods

Theory

In the previous section, the molecular mechanics method was introduced as a procedure for the calculation of some thermodynamic quantity, usually strain energy, for a given system based on a "ball and spring" analysis of nuclear position. Molecular orbital methods, on the other hand, consider the

electronic configuration of a given system. The most widely used ones, the semi-empirical methods, consider electronic interactions of the valence atomic orbitals, while using an empirical or parameterized approach to account for the various interactions of the nuclei and the inner-shell orbitals, or "core". These interactions are a result of approximate solutions to the Schrödinger equation, and themselves may be empirically derived. A discussion of these approximations is beyond the scope of this work.

Applicability and Limitations

Semi-empirical methods have been used for the calculation of heats of formation, ionization potentials, MO eigenvalues and eigenvectors, partial atomic charges, dipole moments⁴⁷. The great advantage of this method over molecular mechanics lies not only in the possibility to calculate this wide range of quantities, but in that the methods are parameterized at the orbital level, and not at the functional group level. That is, the parameters for oxygen are usually transferable to virtually any oxygen, whether it is an ester carbonyl or an alkoxide anion. The accuracy of the method is still sensitive to the choice of the empirical function used and the parameter values chosen, as in molecular mechanics. Another substantial advantage is the ability to calculate

energies for any atomic configuration, ie. the geometry need not be a "stable" or conventional one. This allows the determination of reaction surfaces and transition states for virtually any conceivable reaction.

The great disadvantage of semi-empirical methods, relative to molecular mechanics, is the time required to do a given calculation. Generally, the time required to do one self-consistent field calculation is proportional to the cube of the number of atoms; an analogous calculation using molecular mechanics, say to calculate the steric energy of one conformer, is proportional only to the square of the number of atoms. It is practical to perform the calculation of a reaction coordinate, with full geometry optimization at each incremental step, on systems with fewer than roughly twenty atoms (assuming a moderate computer, such as a Vax 11/780, and a run time measured in hours or days). More complex systems require constraints to limit the number of calculations. These include the specification of symmetry, the fixing of the relative geometry of portions of the molecule, or the relaxation of the stringency with which the energy minimum is determined. Full geometry optimization for a single structure is practical, without constraints, on structures with up to roughly thirty atoms. The presence of an open-shell electronic structure greatly slows the calculation.

Examples of Applications

Aissani et al⁴⁸ challenged the long held view that a carbocation is stabilized by inductively electron donating groups. Using MNDO (Modified Neglect of Differential Overlap), this group showed that the stability of a carbocation is more dependant on electron donation and polarization stabilization; an sp^3 carbon next to a carbocation was found to acquire considerable negative character.

Figure 1

McKee⁴⁹ determined the transition state for the organolithium amination by lithium alkoxamides, using MNDO calculations. Methyl lithium and lithium methylmethoxyamide reacted to give a trigonal bipyramidal transition state (figure 1). This model was then used to calculate the reaction coordinate for

Basis sets

The mathematical description of the orbitals to be used in an ab initio calculation is known as the basis set. These may be STO (Slater Type Orbitals) or GTO (Gaussian Type Orbitals), and may be described by different numbers of functions. For instance, the STO-3G basis set contains orbitals simulated by 3 Gaussian functions. In split valence, or double zeta, basis sets different functions are used for the inner and outer shell orbitals; this allows greater accuracy when doing calculations on diffuse systems, such as charged ones.

Geometry optimizations are usually done using a minimal basis set (such as 3-21G), and the resulting structure examined with a single-point calculation with a larger set (such as 6-31G*)⁵¹. This results from the dependence of the time of computation with the fourth power of the number of basis functions.

RESULTS AND DISCUSSION

The Original TRIBBLE

TRIBBLE⁵² was until recently the main molecular modelling package of the DuPont de Nemours Co. in Wilmington, Delaware. The package consisted (as received) largely of public domain routines available from the Quantum Chemistry Program Exchange (QCPE) at the University of Indiana.

TRIBBLE Programs

a. structure input

TRIBBLE is equipped with GRAFIX, an excellent routine for the input of organic structures. While the trend recently has been to allow structure input in a three-dimensional sense, which the author believes to be cumbersome, GRAFIX uses two-dimensional input. That is, the structure is created in exactly

the way that an organic chemist would represent the structure with pencil and paper. A 2-D input file (z-coordinates all zero) is created by GRAFIX for molecular mechanics optimization, which then allows the molecule to relax into a 3-D structure. A z-coordinate may be specified for any atom, in an attempt to create a desired stereochemistry; this sometimes fails, requiring manual alteration of the structure and reminimization. For an example of GRAFIX, see Appendix A.

b. geometry optimization

TRIBBLE was equipped with two molecular mechanics programs, MM1 and MM2. Both were written by Allinger, the former in 1973 and the latter in 1977⁴⁵. MM2 has been proven superior to MM1⁵³, both for the calculation of conformational energy and heats of formation. Files generated by GRAFIX could originally only be used as input for MM1.

c. MO calculations

1) semi-empirical methods

EHT⁵⁴, CNDO⁵⁵, and INDO⁵⁵ are semi-empirical methods which have fallen somewhat into disuse due to unreliable results (although newer versions of the latter two are used for some limited applications). These, MINDO/3⁵⁶, and an older implementation of MNDO⁵⁷ were included in TRIBBLE, along with a program (OPT9) which would create the input necessary for geometry optimization with all of the above programs. REX⁵⁸ (Relativistically Enhanced Extended Huckel) is one of the few programs which can perform MO calculations on lanthanides and actinides, but suffers from the same limitations of EHT. PPP⁵⁹ (Pariser-Parr-Pople) allows MO calculations for planar pi-systems, but not much else.

2) ab-initio

TRIBBLE was delivered with no source code for any ab-initio program. The executable image for a routine called HONDOG was present; this may be a version of HONDO5 (QCPE 403), but without documentation or source code it is of no value to TRIBBLE.

d. graphic output

1) Pluto

PLUTO was written by Motherwell⁶⁰ for the display of results from x-ray crystallography. Its options include:

- stick, stick-and-ball, or space filling display
- stereo display
- specification of atom radius, bond thickness, bond taper, and light source position
- omission of specified atom types
- rotation around specified axis or bond
- view down specified bond, or orthogonal to three atoms

2) MO, electron distribution, electrostatic interaction, common volume maps

MO and electron distribution maps were calculated by the programs MOPLOT and MOSHOW, derived from the PSI/77 program written by Jorgensen⁶¹. These programs accept MO eigenvectors and overlap matrix

values calculated by EHT, derive psi and psi-squared values for slices through the molecule, and output a three- dimensional, wire-frame surface representing any desired contour level.

Van der Waals interaction maps are created by TRIBBLE by VDWCOMP and VDWPLOT. A test probe of any desired radius and epsilon (or hardness) is "rolled" over the molecule, and the interaction matrix is stored and graphically output using a wire frame representation, in a similar way to the MO's. To represent molecular similarity, molecules may be superimposed and the volume common to them all displayed by BULKCOMP and BULKPLOT. The proper relative orientation is crucial for the generation of meaningful results (see Appendix A)

e. research options

1) structure superimposition

Two levels of structure superimposition exist in TRIBBLE. First, it is possible using CONMRG to merge any number of structure (connectivity, or .CON) files, orienting each structure independently on reference cartesian axes.

Second, OPT9 allows the fitting of structures by specifying atoms to be superimposed. The distances between those atoms is minimized, and it is possible to weight certain atom fits more than others.

2) geometry examination and manipulation

CONEDIT enables the manipulation of .CON files. Atom types, location, and connectivities can be examined and changed; bonds moved, made, or broken; atoms can be added or deleted; atom locations may be switched (to invert chirality) or lone pairs added.

DISTANCE, ANGLE, and DIHEDR are utilities which, as their names imply, allow the calculation of any desired distance, angle, or dihedral angle in a molecule. The atoms examined do not have to be directly bonded. DISTANCE also allows the calculation of the distance from one atom to the geometric mean of a group of atoms (a ring center, for example). See the Tribble tutorial, Appendix A, for examples.

3) determination of chirality

CHIRAL calculates the absolute stereochemistry of all of the chiral atoms in a molecule. Some bridged systems may cause CHIRAL to fail.

4) determination of ring pucker

PUCKER is based on routines written by Pople and Cremer⁶². It calculates the angles of deformation of an atom out of the plane of a ring in terms of phase angle and puckering amplitude; these quantities may be used as parameters in a Hansch structure-activity correlation.

5) calculation of molecular surface area and volume

TRIBBLE contains two routines for the calculation of molecular surface area. AMOLE⁶³ calculates the surface area using numerical integration, while SURFAC uses a Monte Carlo approach.

Molecular volume is estimated by VOLUME, using a Monte Carlo method. A box is created around the molecule, and a million points randomly placed in the box. The ratio of the points inside the molecule (ie. within the

van der Waals radius any atom) to those outside is the same as the ratio of volume of the molecule to the volume of the box. The program assumes atom sizes corresponding to Van der Waals non-bonded contact radii.

LOGP⁶⁴ estimates the lipophilicity of a given compound for use in Hansch QSAR calculations. Examples may be found in Appendix A.

Hardware Requirements

TRIBBLE was designed to be run on the VAX line of computers from Digital Equipment Corporation, using the VMS operating system. It is written completely in Fortran 77, with no assembly level routines, and is therefore relatively portable to other Fortran compilers. The system consists of about 40 megabytes of source code and run units, not including 30 megabytes of graphics drivers (GCS, or Graphics Compatability System). TRIBBLE is run on a VAX 750 with 8 megabytes of RAM and 64 megabytes of virtual memory at the Dept. of Electrical Engineering at Carleton University. As data files accumulate quickly, hard disk storage of at least 200 megabytes is recommended. The development work and calculations included in this thesis

was performed using Tektronix 4014 graphics, DEC VT100, an IBM PC compatible (with VT100 and 4014 emulation), and an Atari 520ST (also with VT100 and 4014 emulation) as terminals.

Vector vs. raster technology

Graphics output devices consist broadly of two types, vector and raster. Generally, the former understands images only in terms of vectors, while the raster device displays an array of points.

The advantage of a vector display is the ease with which complex images may be manipulated. By simple vector transformations, an image consisting of a very large number of vectors may be rotated or moved in real time. That is, the three-dimensionality of an image is always preserved, and so manipulations do not necessarily require complex and time-consuming calculations. Real time manipulation requires that the vector list be redisplayed in less than about 1/25 of a second, which is the limit of discrimination of human vision. Longer times result in flicker, similar to the effect seen in old movies. Another advantage (albeit a two-edged one) is that simple objects may be represented by very short, easily stored vector lists.

The major disadvantage to vector display is its basic inability to represent solid surfaces. Although such surfaces may be written as a dense array of vectors, the enormous vector lists created by such a scheme would not be practical due to the speed at which the vectors can be written.

Raster displays show solid surfaces very well, as any television shows. The real time manipulation of solid objects has until now been difficult and expensive on this type of graphics system. Recently, as the price of computer hardware has plummeted, it has become possible to design raster displays with powerful 3-D capability. By incorporating the ability to display 3-D "primitives", such as a polyhedron, in the graphics hardware, real time manipulation becomes possible. In other words, by shifting the computational load of drawing and shading a 3-D surface to the graphics terminal (which can be quickly done in custom hardware), the main computer engine only has to provide the most basic data about the image. For example, a molecule could be represented by its atomic coordinates, the atomic radii, and the type of primitive to represent each atom; the graphics terminal would handle the spatial manipulation of the coordinates, the drawing and shading of the polygons, and the hidden line elimination (i.e. hidden surfaces are not shown). Raster terminals with real time capabilities are still expensive, but are rapidly becoming

cost effective relative to vector displays. With regard to performance, it is sometimes a problem to represent certain surfaces with the graphics primitives available on a particular terminal.

Graphic Techniques

A graphic image may become so complex that the information contained in it is incomprehensible to the viewer. The use of colour introduces an aspect of order which can untangle even a large DNA fragment (by colour coding specified atoms or bases, for example). Depth-cueing makes objects appear closer to the viewer by shading them brighter, giving an image a greater sense of three dimensionality. As well, the apparent location of the light source can be altered, the shadows revealing subtleties of the object.

Tektronix 4014 standard

The Tektronix 4014 is a monochrome graphics terminal which has been popular since the 1960's. Much of TRIBBLE was designed to output graphics to this type of terminal. Although the image is a high resolution one (1000 x 1000), without colour some of the images produced are confusing and

therefore of limited use (especially the MO maps, to be discussed later). However, the advantage to the Tektronix standard is one of availability. Almost every major graphics terminal and personal computer is capable of emulating, or behaving like a Tektronix terminal. This is paramount in the design of a software package that is to be used by a great variety of researchers, using many types of computer hardware (and having limited funds to invest in new hardware).

TRIBBLE now has the capability to run virtually all of its routines using a Tektronix 4014 terminal or equivalent.

Weaknesses of the Original TRIBBLE

TRIBBLE was delivered from DuPont with a number of weaknesses rendering it useless for the chemist non-expert in quantum chemistry and computing science.

User interface for the chemist

The routine use of a molecular modelling system by the average chemist requires that the software contain an interface, or "front end", to which he can communicate largely in terms of his own area of expertise. This does not imply that there is nothing that he must learn in order to operate the system effectively, but that the capabilities and limitations of the programs themselves must be paramount. The responsibility of the software designer is to overcome the idiosyncrasies peculiar to the hardware and software, and allow them to function in as transparent a manner as possible. This allows the user an intuitive link with the problem at hand.

1. Lack of chemically oriented prompts

Many of the interactive prompts which control program functions were rather cryptic references to commands and options outlined in the original documentation for the program, as supplied by QCPE. These references were not always in chemical terms. For example, the input file generator for MNDO (and other programs which require the input geometry as internal coordinates) asked for the position of the atom to be optimized, and the "type" of geometry to be optimized (ie. bond length, angle, or dihedral angle), by prompting:

INPUT PARAMETERS TO BE OPTIMIZED AS LOCATION, TYPE

Even after using the system for some time it may not be obvious that the system wants the original atom number (as this program inserts dummy atoms and therefore changes the numbering scheme), and that distance, angle, and dihedral angle should be input as 1, 2, and 3 respectively.

Where possible (ie. when the source code was available), prompts in TRIBBLE were modified to be more intelligible to the chemist user.

2. Lack of graphic interface

Most of TRIBBLE's programs require some sort of text based command in order to execute them. While this is a flexible and (for the experienced user) fast way to run a program that has a number of options, it is not the ideal interface for problems which are often, at least in part, graphically oriented. For instance, a routine such as DIHE, which determines the dihedral angle defined by four specified atoms, is run by keying in the atoms in question. If the user does not know the numbering convention for that molecule, he must exit DIHE, enter a display program such as PLUTO, determine the atom numbers, exit PLUTO, and re-enter DIHE. While this does not appear to be an

overwhelming problem, it can become extremely tedious when large numbers of structures are being examined. Furthermore, the same graphic interface could facilitate access to the capabilities of a large number of routines, saving time and computer resources, and increasing the productivity of the user.

3. Lack of error trapping

It is crucial to the proper execution of any program that the input be of an appropriate format and, of course, that it exists in the first place. If this is not the case, then the program will crash. TRIBBLE was delivered with very little error trapping built in. For example, when running an interactive program such as ANGLE, if a text character was input instead of a number, when the atom numbers was prompted for, the program would crash (displaying a system error) and the user would be back at the system level. The waste of time in this example is not great, but when using programs with many prompts with a large number of structures the loss of time and resources can become significant. Error trapping can check keyboard input as it is entered, and simply ask for it again should it be obviously incorrect. The existence of proper input files is another example where error trapping can increase efficiency. When a routine is run, the input file should be checked for; if it does

not exist, it should be automatically created. This is especially crucial when running batch jobs. On a busy computer the time for a batch job to be executed can be measured in hours or even days. If the program fails upon execution because the input did not exist, this queue time is wasted, and the user must again wait in line.

All routines in TRIBBLE were given input file error trapping, and many were also modified to check keyboard input.

Out of date routines

1. MM1

MM1 is the original molecular mechanics routine devised by Allinger⁶⁵. It tries to account for torsional conformation mainly by considering hydrogens to be rather large; this causes gauche-butane to be too stable relative to anti-butane (i.e. hydrogen-hydrogen interactions are too severe relative to carbon-hydrogen interactions). MM1 has been superseded by MM2, which uses van der Waals parameters that are more in agreement with experimental

data on non-bonded interactions; an additional three-fold torsional term (V_3) is used to better account for conformational energies of straight chain alkanes.

2. EHT, CNDO, INDO

An extension of Huckel's treatment of planar pi-systems was introduced by Hoffmann⁶⁶, which allowed the calculation of MO's for non-planar systems, and those with heteroatoms. Called EHT (Extended Huckel Theory) it is subject to the same weaknesses of the original method⁶⁷, giving poor heats of atomization and charge distributions.

CNDO and INDO are semi-empirical approximations of the Hartree-Fock SCF MO approach⁶⁸. As mentioned earlier, these methods assume valence electrons moving over "cores" consisting of nuclei and inner-shell electrons. Even their predecessors, CNDO/2 and INDO/S are prone to large errors in the calculation of heats of formation and charge densities⁴⁴, and so the early versions have been included in TRIBBLE for archival purposes only.

New Routines Implemented

AMPAC

AMPAC (Austin Method PACKage) was recently released to QCPE⁶⁹ by Dewar and co-workers. It is a powerful software system in its own right and is currently the principle source of MO calculations, and data used in routines for the calculation of MO and Van der Waals maps, in TRIBBLE.

1. AM1

The greatest advantage of the AMPAC over the earlier versions of Dewar's semi-empirical MO methods, such as MOPAC (which was released under the same program number as AMPAC), is the AM1 method⁷⁰. AM1 is an extension of the NDDO approximation used in MNDO. A problem with MNDO was the tendency to overestimate the repulsion of two atoms when they are at their van der Waals distance apart. This was overcome in AM1 by the addition of attractive Gaussian terms to the core repulsion function (CRF) for atoms other than oxygen. Heats of formation for highly branched, sterically crowded, and small ring alkanes are significantly more accurate than those

values obtained by MNDO. As well, AM1 seems to reproduce hydrogen bonding, although it does underestimate it somewhat. Heats of formation for anions, cations, and radicals, rotational barriers, ionization energies and dipole moments are all improved relative to MNDO. In fact, Dewar and Storch⁷¹ have shown that heats of formation are generally as reliable from AM1 or MNDO as those calculated by ab-initio methods using the 6-31G* basis set.

2. reaction coordinate calculation

AMPAC has the capability to calculate derive the MO's and related thermodynamic data for a desired reaction coordinate. Selected coordinates may be distance, bonding angle, or dihedral angle, and can be set for any desired range or increment. At each increment all atoms are allowed to relax and, for each increment in the minimization, the entire molecule allowed to come to self-consistency. As a result, this calculation is really only useful in very small molecules.

3. transition state search

The transition state for a given path on a potential surface may be calculated by determining the second derivatives of the molecular energy with

respect to some geometric parameter. The resulting force constant matrix can be diagonalized to give normal vibrations; the transition state is that structure for which there is only one negative eigenvalue in the force constant matrix (ie. vibration). This option is activated in AMPAC by use of the keyword SADDLE.

MM2(80) and MMP2

MM2(80) and MMP2 are the latest versions of Allinger's force field available from QCPE.

MM2(80) is essentially the same as the 1977 version (MM2) with the inclusion of a number of additional parameters, the most important being those for ethers⁷². These were later expanded to try to account for the anomeric effect⁷³.

MMP2 is the version of MM2 used for molecules that have conjugated pi systems. A simple SCF MO routine is used to determine the stretching and rotational parameters for each pi system at the beginning of an optimization run. These parameters are then used by MMP2 in the usual way; if the geometry changes significantly from the original one, the SCF calculation is

repeated (ie. the parameters change dynamically with the change in geometry).

The structure is considered minimized when a new SCF calculation does not change beyond some preset limit from the last run.

DRAW

DRAW⁷⁴ is a graphics package designed to compliment AMPAC by allowing the display of geometries derived from semi-empirical calculations. Three dimensional structures may be produced using one of three representations, namely stick, NAGOYA, and ORTEP. The first is similar to the stick representation produced by PLUTO. NAGOYA output is not as clear as the corresponding PLUTO solid output, but is output at roughly twice the speed. ORTEP structures are well known as the standard representation for three dimensional structure data derived from x-ray crystallography, and are probably the clearest representations produced by a monochrome display; they are, however, also the slowest.

DRAW also contains useful capabilities for the examination and editing of distances, angles, and dihedral angles in a given molecule. Editing is constrained by the manner in which the internal coordinates for the system

where created. That is, only those quantities which are defined by the internal coordinate tree may be changed. Manual editing of the geometry, by explicit specification of new cartesian coordinates, is allowed. Among the modifications made to DRAW were the ability to write a modified structure to a new .CON file, and the ability to use AMPAC input files (.AMI) as input.

As well, DRAW contains some of the standard features of PLUTO, such as the rotation of the whole molecule, and the masking or unmasking of specific atoms. Sample DRAW output may be found in Appendix A.

DRVPLLOT

DRVPLLOT was added to TRIBBLE to allow fast, graphic examination of the results of the dihedral driver option of MM2/MMP2. These energies, stored in .D2H files, may be input for any number of structures; the type of energy to be displayed (ie. stretching, bending, etc.) can be chosen interactively. DRVPLLOT makes use of many of the plotting options found in the GCS library.

MAKECOM command file generator

Each program in TRIBBLE does something different to its input data. There is, however, a regularity to the sequence of operations that must be performed before a program may be successfully invoked. This sequence of operations varies from program to program, but for any one program is unvarying, and is entrenched in a command file. Also, as the types of sequences used by TRIBBLE are fairly rigid, the program to create these command files may itself be entrenched in a command file. Almost all the operation sequences are subsets and optimizations of one general sequence, may be summarized as follows:

1. Determine which molecular structure is to be acted upon;
2. Determine whether all the necessary input files exist;
3. If some of the input files are missing, either create them or give up;
4. Get data values for main program;
5. Execute the main program, either immediately, or queued in the background;
6. If something went wrong with this sequence, write out an error message.

The steps which may be most often omitted are creating the missing input files and interactively getting data values before executing the main program. A large number of programs take a .CON (connection) file as their sole input. It is also not unusual that the various input files taken together will provide all necessary data values, and none need be prompted for. Conversely, the sequence and types of data values for some of the programs are too irregular to be handled by command files, and is best left to the programs to handle directly. Finally, no temporary data or queue files need be created for programs which will obtain their data values interactively. Error messages pertaining to these files need not be included. A fair number of the TRIBBLE command files contain nothing more than a structure name determination, a file existence check, a program execution statement, and an error message.

MAKE utility

The TRIBBLE package is composed of a large number of different programs, each of which must be compiled and linked differently. There is, however, a regularity to the types of operations that must be performed in order to rebuild a program. Furthermore, although the exact sequence of

rebuilding operations varies from program to program, the rebuild sequence for any one program is fixed. Instead, however, of encasing each of the rebuild sequences within its own command file, each of the sequences is encased within a specially formatted data file. These data files, known historically as MAKE (.MAK) files, may be interpreted by the MAKE program in order to rebuild TRIBBLE programs.

In general, the sequence of operations required to rebuild a program is:

1. Create all logical definitions necessary to connect internal file names to their external equivalents;
2. Compile, with the appropriate compiler and options, each of the individual source-language files which make up the program;
3. Link together, with the appropriate options, all of the compiled source files, along with any auxiliary pre-compiled source libraries that may be necessary to complete the program image.

In practice, this sequence might involve compiling a large number of already-compiled source files, or perhaps even recreating an entire program image which need not be recreated. Therefore, the MAKE utility has been implemented such that only those source files which have been altered are

recompiled; if nothing has changed, then the executable image file is not recreated.

MAKE runs as a background process, freeing the terminal for other interactive uses.

DIFFCON

OPT9 has the capability to interpolate between two structures, creating a series of structures intermediate between two; these structures may be examined energetically (to do a quick reaction coordinate calculation, for example), or may be animated graphically using ANIMOL. In order to get meaningful interpolated structures, the atom numbering system must be the same in the initial and final structures, or else atoms would seem to jump from position to position on the molecule. DIFFCON examines the atom connectivity in two specified .CON files, and displays any differences. The atom numbering scheme can then be changed in one of the structures, using the VAX full-screen editor (no dedicated utility exists for this in TRIBBLE).

REPLOT

Originally, the 3-D plotting routines such as MOPLOT were only executable interactively. This created a number of problems. First, if the user was not sure of the orientation of the plot, or if the previous run of MOCOMP was meaningful (due to the wrong selection of contour level or desired MO's, for example), he would have to occupy his terminal for the entire time during which the calculations for the plot were being performed. This criticism is, in fact, valid for all programs which do not operate in batch mode and take more than several seconds to execute. Secondly, and more seriously, was the inability to store a plot once the desired one was obtained. This would have required executing the entire contour calculation, which may have taken up to half an hour and would have required remembering the parameters for the desired viewing perspective, each time one wanted to see the plot.

In order to circumvent the above problems, a new device type is used. By specifying TERM PDF. (Pseudo Device File) at the command level prompt, display commands which normally would go to the display terminal (in this case Tektronix 4014 codes) are diverted to a file. This file may be redisplayed by the routine REPLOT.

Modifications to Existing Routines

SPACE option for PLUTO

PLUTO allowed the display of molecules using either a stick or stick-and-ball approach, but did not permit the easy display of spacefilling models. Since it was possible to vary the size of the atoms in the stick-and-ball display, the atomic radii needed only be set to the non-bonded van der Waals contact radii in order to get a spacefilling model. A list of these radii was added to PLUTO, and the keyword SPACE added to those commands enabled at the PLUTO prompt.

Hidden line elimination optimization

The hidden line elimination routines in the MO and van der Waals map programs (MOSHOW and VDWSHOW) provided with TRIBBLE were those from Jorgensen's PSI77⁶¹ program. These routines were extremely inefficient, taking hours to plot the occupied MO's of a molecule with only 30 or 40 atoms. This was due to the fact that each point in the three-dimensional array was

"clipped" (or compared to see which one was in front) against every other point in the array. This included the points which were found to be hidden. By progressively removing these points from the hidden line elimination, the program executed on the order of 20 times faster.

Least-squares line smoothing for 3-D plots

The above mentioned 3-D plots are all generated from a 3-D array of points through which curves are drawn corresponding to some desired contour level. The fairly high resolution of the array may cause some contours to appear more precise than is possible from the precision of the MO calculation that generated the data. The routine that generates the contours uses an interpolation method, so the generated curve passes through all of the data points. A routine which generates curves using a least-squares method, and not an interpolative one, has been installed into the appropriate routines in TRIBBLE. This allows the generation of smoother curves which are more reasonable reflections of the accuracy of the MO programs, such as AMPAC. Using the least-squares option does slow the 3-D map generation somewhat for small molecules; in large systems (50 atoms) the slowdown can be quite severe.

Applications

In order to demonstrate the ability of TRIBBLE to handle problems in a number of areas, calculations were performed with regards to the following applications:

- the examination of SAR's for the tricothecene family of fungal metabolites.

- the prediction of the possible intermediacy of Bazzanene in the biosynthesis of Tricothecenes-like compounds.

- the calculation of fundamental conformational information for Sialic acids and some derivatives.

- the rationalization of experimental observations with regards to the synthesis of some Dendroprimane precursors

- the synthesis of biosynthetic precursors of Amyryllidaceae alkaloids via transition metal catalyzed Aryl halide couplings

A) Biological Activity of Trichothecenes

The trichothecenes are a group of secondary metabolites produced by a number of fungi genera, including *Fusarium*, *Trichothecium*, *Trichoderma*, and *Cephalosporium*⁷⁵. They are responsible for outbreaks of mycotoxicoses of humans, livestock, and poultry⁷⁶ in a number of grain-related outbreaks of toxicoses in many parts of the world throughout the last century⁷⁷. The toxic effects in man of the fusarial metabolites include fever, hemorrhagic dermal rash, anemia, hemorrhages in the GI tract, necrosis, agranulocytosis, septic angina, and exhaustion of bone marrow⁷⁸.

1. SAR's

Trichothecenes generally possess structures similar to T2 (6) and trichodermol (7). A number of macrocyclic trichothecenes, bearing large rings connecting position 4 to 15 (such as Verrucarin A, 8), have also been isolated⁷⁹.

The principle biochemical effect of the trichothecenes is the inhibition of protein synthesis^{80,81}. There is also considerable interest in the trichothecenes and their macrocyclic derivatives as anti-leukemic agents⁷⁹⁻⁸³, although there is

Figure 2

- not necessarily a correlation between this and their effects on protein synthesis⁸⁴.

The most important functionality on the trichothecenes, with respect to activity, seems to be the 12,13 epoxide^{75,76,85}. Alteration of the epoxide results in a complete loss of bioactivity^{80,81,84}. Epoxide opening in trichothecenes has been shown to occur by three routes (figure 3):

- (1) nucleophilic attack at C-13;
- (2) acid catalyzed ring opening at C-1 and opening of the epoxide, followed by cyclization at C-12, and
- (3) participation of the 9,10 double bond.

Synthetic analogues bearing similar functionality (13-15) have slight

Figure 3

activity against P388 mouse leukemia^{86,87,88}, while those with the inverted epoxide stereochemistry are inactive.

A number of trichothecene derivatives (figure 4) were examined in an attempt to rationalize their activities with respect to protein synthesis inhibition and cytotoxicity to P388 mouse leukemia. Test anti-leukemic molecules were

chosen from studies by Kaneko⁸⁴, who innovated a number of synthetic Anguidine analogues, and Jarvis^{79,89}, who synthesized a number of Verrucarins

13

14

15

and Baccharin analogues; the latter were modelled as the corresponding non-macrocyclic acetates. Wei and McLaughlin⁹⁰ investigated the effects of simpler trichothecenes on protein synthesis.

Molecular mechanics calculations were performed on selected trichothecenes. Three-dimensional structures of low energy conformers, and distance matrices (in Angstroms) for those oxygens with severely restricted mobility, are listed in Appendix B.

A number of SAR's may be identified for the materials tested for anti-leukemic activity (16-19, Appendix B). The Bristol group⁸⁴ observed that a C-3 ketone greatly enhanced activity. Their most active compound, 16, differs from 19, a material found to be inactive by Jarvis⁷⁹, by the presence of this

Figure 4

ketone. The activity of the Verrucarins may require their macrocyclic fragment, yet this may be offset simply by the presence of the C-3 ketone; this has important implications in later test drugs.

Jarvis also demonstrated the importance of oxygen functionality in the A-ring. Comparison of 17 to 18 suggests the importance of a binding site on the face of the A-ring. 17 possesses a rather striking concentration of accessible oxygens in a tightly clustered orientation (Appendix B, structure and accompanying distance matrix). 18, which contains an A-ring epoxide, is inactive. It is significant that all active trichothecenes possess at least a C9-C10 olefin system; Jarvis⁷⁹ also found that C-16 allylic alcohols were highly potent. Superimposition of the active compounds (Figure 4.1) emphasizes the commonality of presence of oxygens or a double bonded system at C8, above the plane of the ring. Both groups also found enhanced activity for enone systems, which would possess greater electron density at C9 (relative to C10), corresponding more closely to the location of activating oxygens. While two of the inactive compounds (see superimposed structures, Figure 4.2) possess a potentially activating A-ring enone, this seems to be insufficient in the absence of oxygen functionality at C-3, such as a C-3 ketone.

Figure 4.1

Superimposed Trichothecene active
antileukemics

Figure 4.2

Superimposed Trichothecene inactive
antileukemits

The availability of the C12-C13 epoxide for attack by biological nucleophiles is highly doubtful; the trajectory of the nucleophile would seem to have to come from within the molecule, and would be especially unimaginable in structures such as 17. If biological alkylation is occurring, it would seem likely that a cationic process is predominant.

The criteria for the activity of trichothecenes in the suppression of protein synthesis seem to be more flexible than those for antileukemic activity⁹⁰. The requirement for a sterically rather large group at C15, such as an acetyl or macrocyclic ring, is not present; 21, with its C15 methyl, is highly active. In contrast to the antileukemics, oxygen functionality, such as an epoxide, on the face of the A-ring, inhibits activity; 25 which is inactive, differs from 21 only by the presence of this epoxide. The spatial requirements for some sort of oxygen at either C3 or C4 is also loose (see superimposed structures, Figure 4.3). Examination of the modelled 3-D structures does suggest, however, that the possibility of an oxygen existing near, or possibly co-binding with, the C12-C13 epoxide oxygen is a requirement (Figure 4.4). This model does not explain why acetylation of 23 results in an active material, 22.

Superimposed Trichothecene active
protein synthesis inhibitors

Figure 4.3

Figure 4.4

Superimposed Trichothecene inactive
protein synthesis inhibitors

B) Biosynthesis of Trichothecenes

The biosynthesis of Trichothecenes, via the crucial intermediate Trichodiene (25.1), has been reviewed by several workers^{90a-c}, and the exact mechanism of Trichodiene biosynthesis determined elegantly by Cane et. al.^{90d}. Another naturally occurring material related to Trichodiene is Bazzanene (25.2), which possesses the opposite configuration at the carbon which becomes the Trichothecene C6, relative to Trichodiene. The corresponding

Trichothecene-like skeleton (25.3), resulting from the cyclization of Bazzanene, had never been isolated; this is possible either due to the stereospecificity of an enzyme participating in the cyclization step, or due to the inability of the material to cyclize based on the thermodynamic inaccessibility of the product.

Theoretical Bazzanene cyclization product

The structure of the cyclization product from Bazzanene was determined by MMP2 minimization. The resulting molecular mechanics energy, 156.8 kcal/mole, is far too high a value for a stable material; massive distortion normal geometry is clearly visible upon examination of the 3-D structure (Figure 4.1). —Clearly the formation of this material is diallowed purely on thermodynamic grounds.

The experimental verification of this prediction was performed in the laboratory of Dr. R. Greenhalgh, at Agriculture Canada, Ottawa, Ontario, Canada. A culture of *Fusarium Culmorin*, grown in the presence of a mixture of Trichodiene and Bazzanene, resulted in the isolation of the usual Trichothecene products and the re-isolation of the provided Bazzanene. There is some preliminary evidence of oxygenation of the Bazzenene without cyclization.

C) Sialic acid derivatives

α -D-N-Acetyl neuraminic acid, or sialic acid (26, R=H), located at the non-reducing end of the carbohydrate chain in gangliosides, plays a role at the receptor site for cholera toxin⁹¹, thyrotropin⁹², leutinizing hormone⁹³, and

human chorionic gonadotropin⁹⁴. Studies to determine the crystal^{96,97} and solution^{97,98} conformations have been performed, but more fundamental data is necessary to find the SAR's of sialic acid and its derivatives.

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MMP2 calculations were performed on both the α and β configurations of sialic acid and its methyl glycoside (26, $R = CH_3$). Heats of formation and atomic charge were determined by single point MNDO calculations, and barriers to rotation were estimated by the dihedral angle driver option in MMP2.

1. Conformations: Theoretical vs Experimental

Predicted low-energy conformations of all of the compounds examined agreed closely with X-ray and 1H NMR data^{98a}; the geometry matching was especially good for the ring and glycerol side chain. Theoretical dihedral

angles matched well with those calculated from ^1H NMR coupling constants for both α and β configurations. For example, $J_{\text{H6-H7}}$ was found to be 1.9 for the α -anomer and 1.0 for the β . This corresponds well to the calculated dihedrals of 58° and 63° respectively.

Estimation of the rotational barriers of the side chain, and the flexibility of the ring, suggest that the molecule may be relatively flexible. This conflicts with results based on T1 data, showing similar flexibility of the side chain and the ring. These workers had no direct data on the flexibility of the ring, and may have incorrectly assumed the side chain to be very rigid, based on the unsubstantiated assumption that the ring is very rigid.

The barrier to rotation of the amide C-N bond was similar using MMP2 or MNDO (~ 19 kcal); however, MNDO favoured the cis configuration by ~ 4 kcal, whereas MMP2 favoured the trans configuration by ~ 1 kcal. Amide molecular mechanics parameters used were designed for the MM1 force field⁹⁹, but in this instance seem to transfer well to MMP2 as the calculated orientation is that found in the crystal structure. The trans geometry in solution was substantiated by the lack of NOE between the amide methyl hydrogens and H5, which would sit within $2\text{\AA}$ in the cis conformation. As well, the MMP2 calculations correctly simulate the preferred hydrogen bonding of the amide

Beta.Sialic acid, low energy conformer

alpha Sialic acid methyl glycoside
low energy conformer

beta Sialic acid methyl glycoside
low energy conformer

carbonyl oxygen with the C4 hydroxyl hydrogen, instead of the C7 hydroxyl hydrogen.

2. prediction of pK_a by MNDO calculations

The corresponding carboxyl anion for each of the analogues modelled was simulated simply by removing the acid proton from the molecular descriptor file. This assumption is probably a valid one, as Na NMR studies show that the deprotonated acids do not associate with a counter ion^{98a}. MNDO calculations suggest that the ΔH_f of the anions are as much as 21 kcals more stable than the neutral species, correctly predicting the high acidities of these acids (Table 1). As well, examination the $\Delta\Delta H_f$ correctly predicts the greater acidities of the α analogues.

	ΔH_f neutral	ΔH_f anion	$\Delta\Delta H_f$	pK_a
SIAB	-335.5	-349.9	14.4	2.6
SIGB	-318.7	-334.9	16.2	2.4
SIGA	-312.9	-333.9	21.0	1.9

SIAB - sialic acid, beta anomer

SIGB - sialic acid methyl glycoside, beta anomer

SIGA - sialic acid methyl glycoside, alpha anomer

TABLE 1. Predicted pK_a vs. Exptl. pK_a for sialic acid derivatives

3. dependence of ^1H NMR shifts on charge density

The change in the chemical shift, for the protons in the parent acids relative to the deprotonated form, was compared to the change in charge density as calculated by MNDO.

	Charge Density		CD	shift
	neutral	anion		
Sialic acid, beta anomer				
H3-ax	+ 0.0551	+ 0.0409	+ 0.0102	+ 0.078
H3-eq	+ 0.0551	+ 0.0419	+ 0.0134	+ 0.122
H4	+ 0.0122	+ 0.0002	+ 0.0120	-
H5	+ 0.0760	+ 0.0708	+ 0.0052	+ 0.031
H6	+ 0.0239	+ 0.0103	+ 0.0791	+ 0.084
H7	+ 0.0592	+ 0.0346	+ 0.0246	+ 0.061
H8	+ 0.0532	+ 0.0782	-0.0250	-0.010
H9	+ 0.0007	-0.0080	+ 0.0087	+ 0.017
H9'	+ 0.0009	+ 0.0047	+ 0.005	+ 0.000
NHCOCH ₃	+ 0.0203 (av.)	+ 0.0123 (av.)	+ 0.0080	+ 0.006
Sialic acid methyl glycoside, beta anomer				
H3-ax	+ 0.0553	+ 0.0453	+ 0.0100	+ 0.155
H3-eq	+ 0.0478	+ 0.0355	+ 0.0123	+ 0.059
H4	-0.0056	0.0047	+ 0.0009	+ 0.052
H5	+ 0.0761	+ 0.0708	+ 0.0058	+ 0.048
H6	+ 0.0355	+ 0.0223	+ 0.0132	+ 0.088
H7	+ 0.0591	+ 0.0346	+ 0.0245	+ 0.066
H8	+ 0.0562	+ 0.0823	-0.0261	-0.022
H9	+ 0.0003	-0.0084	+ 0.0087	-0.011
H9'	+ 0.0080	+ 0.0038	+ 0.0042	+ 0.004
NHCOCH ₃	+ 0.0204 (av.)	+ 0.0125 (av.)	+ 0.0079	+ 0.012

2

OCH ₃	+0.0026 (av.)	-0.0153 (av.)	+0.0179	+0.097
Sialic acid methyl glycoside, alpha anomer				
H3-ax	+0.0605	+0.0154	+0.0451	+0.174
H3-eq	+0.0418	+0.0302	+0.0116	-0.049
H4	+0.0127	+0.0285	-0.0158	
H5	+0.0908	+0.0718	+0.0190	+0.080
H6	-0.0046	+0.0223	-0.0269	+0.154 <-----
H7	+0.0225	+0.0032	+0.0192	-0.021 <-----
H8	+0.0413	+0.0443	-0.0030	-0.007
H9	+0.0065	-0.0047	+0.0112	+0.006
H9'	+0.0342	+0.0194	+0.0148	+0.000
NHCOCH ₃	+0.0207 (av.)	+0.0127 (av.)	+0.0080	+0.002
OCH ₃	+0.0024 (av.)	-0.0159 (av.)	+0.0183	+0.076

Table 2. Correspondence of change of ¹H NMR chemical shift with change in charge density

For α -sialic acid, the magnitude of the change is not predicted well, but the direction of the change in chemical shift is correct for all of the protons. In fact, the correlation of change in charge density with the direction of the shift may be a sensitive probe for the determination of the rotameric conformation of the C17 carboxyl in sialic acid. The conformation for which the direction in shift matches the predicted charge densities corresponds to the predicted energy minimum for the rotation of that dihedral as calculated by the dihedral driver option of MMP2, ie. the one in which the O6-C5-C17-O19 dihedral angle is ~ 240 degrees, and does not match when that angle is set to that observed in the crystal structure ($\sim 135^\circ$). A similar relation was found for the methyl glycoside of β -sialic acid, although the relation did not correctly predict the

beta Sialic acid MIP2 steric energy vs. 06-C15-C17-019 dihedral angle

alpha Sialic acid methyl glycoside MMP2 steric energy vs.
06-C15-C17-019 dihedral angle

beta Sialic acid methyl glycoside MMP2 steric energy vs.

06-C15-C17-019 dihedral angle

direction of shift for one of the C-9 protons. As well, the relation broke down for H6 and H7 of the methyl α -glycoside. The relation of charge density to chemical shift is reasonable for hydrogen¹⁰⁰, whose local charge density is largely determined by diamagnetic factors and to a much lesser extent by paramagnetic ones. This is not true for carbon, and so a corresponding study using ^{13}C shifts is not possible.

D) Dendroprimane synthesis

Dendroprimanes are a family of natural products which include the trail pheromone in Pharaoh ants¹⁰¹. Successful large-scale synthesis of this material (eg. 27) would result in the control of this insect, by leading them away from areas normally damaged by their foraging.

Weinreb and co-workers¹⁰² described one of the syntheses of δ -conineine (27.1), which is the simplest indolizidine skeleton.

This group created the bicyclic system via a Diels Alder approach, as in scheme 1.

A similar synthetic entry into the dendroprimanes involves the condensation of an N-acyl imine with a diene, catalyzed by the presence of

acids. It is known that acyl ammonium salts are present, and the condensation is believed to occur via stepwise cationic addition rather than a Diels Alder

Scheme 1

process^{102a}. This strategy prompted¹⁰³ the synthesis of Gephyrotoxin (27.9), according to Scheme 2.

The reaction of the acyl ammonium salt derived from 5-ethoxy-2-pyrrolidinone (27.6) with a variety of dienes gives varying yields of cyclized and non-cyclized materials¹⁰³ (figure 11). The rationalization of these results by the examination of the relative stabilities of key intermediates was undertaken in an attempt to better understand the mechanism involved in the synthetic sequence.

	<u>Cyclized</u>	<u>Uncyclized</u>
trace	?
trace	80%
11%	57%
>70%	<5%
trace	75%

Product yields for condensation of
acyl imine with various dienes

Figure 11

1. acyl imine and diene condensation

a. head or tail specificity,

The reaction of 5-ethoxy-2-pyrrolidinone with isoprene in the presence of

formic acid occurs with attack on the head, rather than the tail, of the diene system, resulting in the formate ester 28. The relative energies of cations 29 and 30 were determined by performing single point AM1 calculations on

Head vs. tail cationic addition

Figure 12 .

geometries minimized by MMP2; the intermediate 29 was calculated to be

more stable by about 6 kcal/mole, which would account for the observed predominant product.

b. rotamer populations of dienes

Using a similar method as in the case above, the conformational energies of a variety of dienes were minimized using MMP2, and the heats of formation of the final geometries calculated using AM1. In all cases but that of 2,3-dimethyl-1,3-butadiene the trans geometry is slightly favoured (figure 13). In one mechanism, attack of the ammonium ion on the dienes results in various allylic cations whose cis-trans ratios are determined by that of the starting diene. Examination of the barriers of rotations of the resulting cations suggests that these materials would not be subject to free rotation, and that only the cis products would result in cyclized materials. Since the percentage of cyclized material is not related to the relative amount of cis diene, this is not a likely mechanism. Alternately, it was proposed that the relative stabilities of the allylic cations was responsible for the observed products. Again calculation suggests (figure 14) that this is not the case, as most of the trans cations are slightly more stable, according to AM1 heats of formation, than the cis.

Edwards and co-workers¹⁰³ have invoked secondary orbital interactions

Diene heats of formation
Cis vs. trans rotomer

Figure 13

as a means to rationalize the stabilization of the endo attack of the diene by the acyl ammonium ion. This effect unfortunately would be poorly reproduced by semi-empirical calculations, and ab-initio calculations are out of the question for a molecule of this size.

Cationic addition product rotomers,
heats of formation and barrier to rotation

Figure 14

D) Formation of Cyclobenazaundecines

The free-radical cyclization of the norbelladine (31) analogues proposed to be the primary path of the biosynthesis of the *Amaryllidaceae* alkaloids,

such as lycorine (32). Work in our laboratory¹⁰⁵ has been aimed at the biomimetic cyclization of compounds such as 31 using vanadium reagents on solid phase immobilized substrates (see chapter two). Attempts at the possible synthesis of *Amaryllidaceae*-like compounds via transition metal catalyzed Ullmann or Kharasch reactions (Figure 15) met with failure (for a detailed account, see chapter 2). Subsequently, it was decided to try to explain the reluctance of the reaction using conformational energies calculated by MMP2 and AM1.

Figure 15

The starting material and product in figure 15 were substituted with the corresponding acetamides (35 and 36) for the sake of AM1 calculations, due to the inability of AMPAC to handle d-orbitals¹⁰⁶. Molecular mechanics MMP2 geometry optimizations were performed, and the minimum energy conformer

subjected to single-point AM1 calculation. The steric energy for the starting material and cyclized product by MMP2 were 9.2 and 25.27 kcal/mole

respectively; AM1 heats of formation were -84.67 and -48.67 kcal/mole respectively. Examination of the detailed MMP2 output revealed a large degree of distortion of the aromatic systems in 36 as seen by the rather large 1,4 van der Waals interactions of carbons in the para orientation (up to 1.0 kcal/mole per 1,4 interaction). The energy corresponding to the large conformational barrier to cyclization (up to 36 kcal/mole by AM1 calculation) must be provided in the cyclization process by whatever reactive intermediate is involved. Direct

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calculation of the heat of formation of the transition metal complex intermediate (such as 37) is unreliable due to insufficient parameterization of MNDO level calculations, and impossible at the Gaussian 80 level due to insufficient computer resources for the optimization of such a large system. These restrictions render this kind of analysis impossible.)

In order to circumvent the necessity of calculating the heats of formation of the exact intermediates in the cyclization reaction, it was decided to make assumptions regarding the probable geometry of the system during the cyclization process. Free radical cyclization of phenols has been demonstrated to occur with the aromatics in a stacked orientation¹⁰⁷ (see Appendix C, scheme 2). 35 was oriented in order to have the required stacked orientation for cyclization, and MMP2 minimization performed, without allowing movement of the aromatic carbons (Figure 16). The steric energy of 17.8 kcals (relative to 9.2 kcals for the fully relaxed material) indicates that the required transition state for cyclization is not significantly inhibited by conformational factors. In the case of the Nickel catalyzed reaction, it is well known¹⁰⁸ that ortho groups greatly inhibit the rate of cyclization; this suggests that an edge-on orientation of the bonding aromatic systems is likely. The strain energy of such a system was simulated by modelling the uncyclized material 35 with the hydrogens removed (ie. no atoms attached to the carbons at the bonding site, to prevent Van der Waals interaction there), and again locking the orientations of the aromatic rings before allowing MMP2 geometry optimization. The energy of this system, 164.4 kcals, is clearly prohibitive relative to an accessible low energy conformation. This analysis suggests that, in this case, not only is Van der Waals interference likely from the ortho groups, but that ring strain will

Calculated minimum MMP2 steric energy,
cyclobenzazaundecine model

Cyclobenzazaundecine model,
stacked transition state

Cyclobenzazaundecine model,
edge to edge transition state

prevent the reaction from occurring. This also suggests that the VOCl_3 catalyzed reaction also occurs via a stacked reaction intermediate.

SUGGESTIONS FOR FUTURE RESEARCH

TRIBBLE is (along with MOLY, from Rohm and Haas) the first comprehensive molecular modelling software package available from QCPE. Although many of the shortcomings of the original version from DuPont were improved, recent hardware and software developments could be incorporated into the system, enabling capabilities only available in commercial packages costing tens of thousands of dollars or more.

In order to better interact with the casual user, an improved graphic interface is required. Pull-down menus, accessible using a mouse, would speed the use of system utilities and improve the users understanding of system options. For instance, to calculate a given dihedral angle in a particular structure, the atoms of that dihedral could be selected using the cursor (controlled by the mouse), and the "calculate dihedral" option selected (again with the mouse). It would be unnecessary to invoke PLUTO, select the

structure, determine the required atom numbers, exit PLUTO, select DIHE, again indicate the structure, and input the atom numbers. The user would be more productive, and the chance of user error would decrease. Possible graphic interfaces include the soon-to-be-released XWINDOWS standard (for VAX VMS), or the graphics standards (including GKS) used by APOLLO computers.

Another broad area for improvement is the need for a facility to examine the results that are generated by TRIBBLE without the need to manually examine output files. This would allow the direct comparison of chemical data for a number of compounds, making it easier to spot trends in characteristics, or user error. Ideally the user would be able to save the profile of the types of characteristics queried and the compounds examined, and the tabulated data stored as data files for later reference and report writing.

The ability to systematically search for accessible conformations (as in the active analogue approach used in SYBIL¹⁰⁹) has traditionally been done by driving dihedral angles incrementally through the desired ranges and doing a full geometry optimization at each stage. Where R is the number of increments per bond and M is the number of rotatable bonds, this would generate R^M optimizations. For a flexible system this kind of search is prohibitive in terms

of computer time. Recently, the distance geometry, or pure central force field, method has been used to allow this kind of analysis¹¹⁰⁻¹¹². This approach is a molecular mechanics method using a force field with only distance terms. For instance, the angle parameter in MM2 has been replaced with a 1,3 distance term. This approach removes the necessity to calculate internal coordinates from cartesian coordinates, and results in a significant (2-10 fold) increase in execution speed. The number of accessible conformers may be constrained by specifying chirality or the inclusion of other distance data such as NOE results¹¹³.

The determination of a pharmacophore hinges on the ability to determine common characteristics of a group of active compounds. It is therefore useful to be able to calculate the commonality of such characteristics, such as electrostatic charge or van der Waals interaction, with respect to the allowed conformations, in order to find common electronic and physical properties in a spatial sense. The commercial packages SYBIL and CHEM-X¹¹⁴ have this capability; in the long term, it is essential for TRIBBLE.

A number of programs have been released by QCPE which are capable of the analysis of spectral data or spectral simulation. These programs would

routinely be of great benefit to synthetic organic chemists. Some of them are presented in the following table:

NAME	QCPE Number	Function
PAIRS	497	analysis of IR spectra
DOKI77/78	519	NMR spectra simulation
DAISY	518	NMR simulation and analysis
DSYMLOT	470	NMR simulation in isotropic and anisotropic phases
NMR	456	interactive NMR simulation
MIMER	394	NMR simulation
DAVINS	378	Direct analysis of very intricate NMR spectra

Finally, a number of programs, such as LHASA¹¹⁵, capable of suggesting syntheses of a desired compound are currently available. This capability in TRIBBLE would help chemists solely interested in synthesis, as well as the medicinal chemist who must synthesize a proposed drug for biological testing.

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APPENDIX A

A TRIBBLE Tutorial

The quality of this microfiche is heavily dependent upon the quality of the thesis submitted for microfilming.

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AVIS

***** TRIBBLE Molecular Modeling System *****

Version 4.0

This version of TRIBBLE has been made possible by

Lee Herman (Chemistry)
Walter Robertson (Programming)
J. W. ApSimon (Financial Support)

at the Ottawa Carleton Institute of Chemistry,
Carleton Campus, Ottawa, Ontario, Canada

based on the original system by Dave Popzak, John Wendoloski, and
Zelda Wasserman of E. I. DuPont de Nemours & Co., Wilmington, Delaware

Now installing TRIBBLE definitions

Terminal type (AED ID100 PDF RFI V1100 ZETA 4010 4014 *none*) | VT100 | 4014

\$ GRAPHX EXAMPLE

**** Executing GRAPHX

**** (Note: User input may be required here)

**** File TRNSEM.DAT fetched from TRNLIBRARY

100 YOU HAVE A TABLET (Y/N)?

CUTOFF
RATING

↑

25

↓

1 CRT

2 NODE

STORE

DRAW

END

MOVE

HELP

DELETE

SCAN

WIPE

TREE

STEREO

PROCESS

SKETCH2

SMALL

AXL EQU

AXL EQU

AXL EQU

AXL EQU

AXL EQU

AXL EQU

AXL EQU

AXL EQU

AXL EQU

AXL EQU

CURSOR
RATING

1xCR1
2xCR2

STORE
DRAW

END
MOVE

HELP
DELETE

SCAN
WIFF

TREE
STEREO

PROCESS
SKETCH2

H

O

N

C

P

S

F

CL

RJ

a

e

CURSORSTRAT

AXL-EQU

ATOM NO

BOND NO

SMALL

STRUCTURE NAME -example
Z MODIFY 1
Z = 1
Z MODIFY
ID STRING tutorial example
ARE ANY CONSTANTS TO BE READ IN (1 - YES) 1
\$ mm2 example
DRIVE A DIHEDRAL ANGLE (N)
INTERACTIVE OF BATCH 1 BATCH 1 1
INPUT FILE -
OUTPUT FILE -

INITIAL STERIC ENERGY IS 582 4204 KCAL

COMPRESSION 109 8464
BENDING 745 5956
STRETCH BEND 62 1596
VANDERWAALS
1.4 ENERGY 5 6728
OTHER 0 0900
TORSIONAL 1 2479

TOTAL ENERGY IS 582 4204 KCAL
COMPRESSION 109 8464
BENDING 745 5956
STRETCH BEND 62 1596
ITERATION 1
ITERATION 2
ITERATION 3
ITERATION 4
ITERATION 5

TOTAL ENERGY IS 203 2174 KCAL
COMPRESSION 6 0407
BENDING 272 9215
STRETCH BEND 4 9334
ITERATION 6
ITERATION 7
ITERATION 8
ITERATION 9
ITERATION 10

TOTAL ENERGY IS 283 2074 KCAL
COMPRESSION 6 0290
BENDING 272 9531
STRETCH BEND 4 9895
ITERATION 11
ITERATION 12
ITERATION 13
ITERATION 14
ITERATION 15

TOTAL ENERGY IS 283 1724 KCAL
COMPRESSION 6 1052
BENDING 272 8247
STRETCH BEND 4 0388
ITERATION 16
ITERATION 17
ITERATION 18
ITERATION 19
ITERATION 20

TORSION 3 2479
DIPLE/CHG 0 0000

TORSION 3 3143
DIPLE/CHG 0 0000

TORSION 3 3267
DIPLE/CHG 0 0000

TORSION 3 4026
DIPLE/CHG 0 0000

1196	VANDERWAALS	279	0246	KCAL					
COMPRESS	7	7259	VANDERWAALS						
BENDING	26	4902	1.4						
STR BEND	5	3131	OTHER	4	9408	TORSION	4	9408	0.0000
ITERATION	21		AVG MOVEMENT	0	1141	DIPL/CHG	0	1141	
ITERATION	22		AVG MOVEMENT	0	02709	A			
ITERATION	23		AVG MOVEMENT	0	04105	A			
ITERATION	24		AVG MOVEMENT	0	04451	A			
ITERATION	25		AVG MOVEMENT	0	04326	A			
ITERATION	25		AVG MOVEMENT	0	04188	A			
TOTAL ENERGY IS	279	0246	KCAL						
COMPRESS	7	7259	VANDERWAALS						
BENDING	26	4902	1.4						
STR BEND	5	3131	OTHER	4	9408	TORSION	4	9408	0.0000
ITERATION	26		AVG MOVEMENT	0	04723	A			
TOTAL ENERGY IS	272	1236	KCAL						
COMPRESS	8	6079	VANDERWAALS						
BENDING	26	19609	1.4						
STR BEND	6	0486	OTHER	4	0097	TORSION	4	0097	0.0000
ITERATION	27		AVG MOVEMENT	0	00960	A			
TOTAL ENERGY IS	263	2063	KCAL						
COMPRESS	7	6273	VANDERWAALS						
BENDING	25	8973	1.4						
STR BEND	6	0205	OTHER	4	2366	TORSION	4	2366	0.0000
ITERATION	28		AVG MOVEMENT	0	00009	A			
TOTAL ENERGY IS	254	3140	KCAL						
COMPRESS	7	3496	VANDERWAALS						
BENDING	24	6716	1.4						
STR BEND	6	1063	OTHER	3	5387	TORSION	3	5387	0.0000
ITERATION	29		AVG MOVEMENT	0	01155	A			
TOTAL ENERGY IS	247	1690	KCAL						
COMPRESS	7	0685	VANDERWAALS						
BENDING	24	0117	1.4						
STR BEND	5	9554	OTHER	2	9691	TORSION	2	9691	0.0000
ITERATION	30		AVG MOVEMENT	0	02986	A			
TOTAL ENERGY IS	243	2171	KCAL						
COMPRESS	6	8321	VANDERWAALS						
BENDING	23	8597	1.4						
STR BEND	5	7495	OTHER	2	4969	TORSION	2	4969	0.0000

*** MINIMIZATION CANNOT CONTINUE DUE TO ABNORMAL BOND LENGTH ***

FINAL STERIC ENERGY IS 241.95/4 KCAL

COMPRESSION	5	5724
BENDING	23	8598
STRETCH BEND	5	7495
VANDERWAALS	2	4969
1.4 ENERGY	0	1313
OTHER	1	9092
TORSIONAL		
PORTMAN STOP		

pluto example
**** Generating PLUTO input file
**** (Note: User input may be required here)
**** Executing CONPLU
**** (Note: NO user input expected here)
STRUCTURE NAME =
**** Executing PLUTO
**** (Note: User input may be required here)

PLUTO>file example
PLUTO>plot

PLUTOGRAPH
PIROGRAPH

TUTORIAL EXAMPLE

PLUTO00X11

PI PORTAL EXAMPLE

```

$ conali example
**** Executing CONALI
**** (Note: User input may be required here)
STRUCTURE NAME -example
MODIFY CHARGE ON ATOM NO.
GENERATE NEW HYDROGEN COORDINATES [N] Y
TITLE [example]
ARE ANY CONSTANTS TO BE READ IN [Y] ?
MAXIMUM EXECUTION MINUTES? [program default]
NUMBER OF RESTRICTED MOVEMENT ATOMS
INITIAL ENERGY ONLY [N]
FOR MM2 OR MM2 [MM2]
IS THIS STRUCTURE A POLYNUCLEAR AROMATIC (Y/N)? [N]
EXACT VAN DER WAALS CALC [Y] N
$ mm2 example
DRIVE A DIHEDRAL ANGLE? [N]
INTERACTIVE OR BATCH [ BATCH ]
Job EXAMPLE (queue SYSSBATCH, entry 1703) started on SYSSBATCH
$ q
Batch queue SYSSBATCH
$ type example.m2c
0 FINAL STERIC ENERGY IS 8.640/ KCAL.
COMPRESSION 0.0675
BENDING 0.5275
STRETCH BEND 0.0196
VANDERWAALS 0.4245
1,4 ENERGY 0.0290
OTHER 7.7098
TORSIONAL 0.0000
DIPOLE 0.150 D
0 DIPOLE MOMENT
0 COMPONENTS WITH PRINCIPAL AXES
X 0.1309 Y 0.0010 Z 0.0732
0 END OF example
FIXED 0 0 0 0 0 0 0 0 0 0 0 0
$ pluto example
EXAMPLE pluto is obsolete. Rebuild it [YES]
**** Generating pluto input file
**** (Note: User input may be required here)
**** Executing CONALI
**** (Note: No user input expected here)
STRUCTURE NAME
**** Executing PLUTO
**** (Note: User input may be required here)

```

PLUTO>view matrix x101 30
PLUTO>plot

EXAMPLE

pluto>space
pluto>plot

EXAMPLE

PLUTOexit

EXAMPLE

EXAMPLE

EXAMPLE

PLUTO>

```

$ type example con
10example 4 454864 4 227204 0 17596H 1 2 5
C 2 5.320918 5 469610 0 218277 22 1 3 4
C 3 6.703825 5 376817 0 384045 22 2 4 9
O 4 5.598897 6 054684 1 13699H 22 2 3 10
H 5 4.541269 3 672614 1 117910 3 1 1
H 6 4.748778 3 547819 0 655940 5 1 1
H 7 3.390444 4 517571 0 024402 5 1 1
H 8 5.083548 6 238812 0 950387 5 2 2
H 9 7.472458 6 070564 0 054870 5 3 3
H 10 7.034305 4 458948 0 862111 5 3 3

```

```

$ dihe example
**** Executing DIHEM
**** (Note: User-input may be required here)
STRUCTURE NAME -example
INPUT THE FOUR ATOMS OF THE DIHEDRAL 1,2,3,4
DIHEDRAL IS 156.714
INPUT THE FOUR ATOMS OF THE DIHEDRAL

```

```

$ conali example
**** Executing CONALI
**** (Note: User-input may be required here)
STRUCTURE NAME -example
MODIFY CHARGE ON ATOM NO
GENERATE NEW HYDROGEN COORDINATES [N]
TITLE [example]
ARE ANY CONSTANTS TO BE READ IN [Y]
MAXIMUM EXECUTION MINUTES? [program default] 120
NUMBER OF RESTRICTED MOVEMENT ATOMS
INITIAL ENERGY ONLY [N]
FOR MM2 OR MM2 [MM2]
IS THIS STRUCTURE A POLYNUCLEAR AROMATIC (Y/N)? [N]
EXACT VAN DER WAALS CALC [Y] n

```

```

$ mm2 example
DRIVE A DIHEDRAL ANGLE? [N] Y or 160* (N) OR free chain (Y)? [N]
Angle in ring may not pass 0 or 160*
FIRST DRIVEN ATOM? 1
SECOND DRIVEN ATOM? 2
THIRD DRIVEN ATOM? 3
FOURTH DRIVEN ATOM? 9
STARTING ANGLE? 156
ENDING ANGLE? 180
ANGLE INCREMENT? 3
INTERACTIVE OR BATCH [ BATCH ]
Job EXAMPLE (queue SYSS$BATCH, entry 1/05) started on SYSS$BATCH

```

```

$ q
Batch, queue SYSS$BATCH
Jobname Username Entry Status
EXAMPLE USERC 1/05 Executing
$ dplot example

```

PLUTO

NEWEXAMPLE

```

$ distance example
*** Executing DISTANCE
*** (Note: User input may be required here)
STRUCTURE NAME -example
FIRST ATOM(S) - 2
SECOND ATOM(S) - 3
DISTANCE - 1.5112
FIRST ATOM(S) - 2
SECOND ATOM(S) - 4
DISTANCE - 1.5021
FIRST ATOM(S) -
$
$ angle example
*** Executing ANGLE
*** (Note: User input may be required here)
STRUCTURE NAME -example
ATOM NUMBERS - 2,3,4
ANGLE IS - 59.864
ATOM NUMBERS - 1,2,3
ANGLE IS - 117.491
ATOM NUMBERS -
$
$ dihe example
*** Executing DIHEDR
*** (Note: User input may be required here)
STRUCTURE NAME -example
INPUT THE FOUR ATOMS OF THE DIHEDRAL 1,2,3,4
DIHEDRAL IS ( ) 102.588
INPUT THE FOUR ATOMS OF THE DIHEDRAL
$

```

```

$ VOLUME EXAMPLE
**** Executing VOLUME
**** (Note: No user input expected here)
INPUT STRUCTURE NAME = 3744/ d5968
POINT RATIO = 74 88 ANG**
THE VOLUME IS 1.000

$ SURFAC EXAMPLE
**** Executing SURFAC
**** (Note: User input may be required here)
STRUCTURE NAME = EXAMPLE
ATOM - 1 FREE AREA = 28 27 EXPOSED 0 75
ATOM - 2 FREE AREA = 50 27 EXPOSED 10 23
ATOM - 3 FREE AREA = 50 27 EXPOSED 12 61
ATOM - 4 FREE AREA = 50 27 EXPOSED 5 44
ATOM - 5 FREE AREA = 32 17 EXPOSED 2 67
ATOM - 6 FREE AREA = 32 17 EXPOSED 5 20
ATOM - 7 FREE AREA = 32 17 EXPOSED 16 67
ATOM - 8 FREE AREA = 32 17 EXPOSED 0 00
ATOM - 9 FREE AREA = 32 17 EXPOSED 8 94
ATOM - 10 FREE AREA = 32 17 EXPOSED 5 20
THERE WERE 138945 ITERATIONS
$document {language tektronix,
  imagesize (8.50 5.75),
  window (9.00 6.25),
  at (1.50 10 cc)}
$ ANGLE EXAMPLE
**** Generating ANGLE input file
**** (Note: User input may be required here)
Solvent Radius 1 0 1 1 0
**** Executing CONMOL
**** (Note: No user input expected here)
STRUCTURE NAME =
SOLVENT RADIUS =
**** Executing ANGLE
INTERACTIVE OR BATCH 1 BATCH 1 1
**** (Note: No user input expected here)
STRUCTURE NAME =
ATOM NUMBER 1 PERCENTAGE 0 116
XXXXX IS 1 0674117
1 8 NNNN 4 RACT 2 7 00 P(1,1) 1 502 RA(NNNN) 1 000
GEOMETRY OF STRUCTURE TOLENT WORK ALGORITHM
FORTRAN STOP
$ ANGLE EXAMPLE
**** Executing ANGLE
INTERACTIVE OR BATCH 1 BATCH 1
Job EXAMPLE (queue SYSSBATCH entry 1040) terminated SYSSBATCH
$ Q
Batch queue SYSSBATCH
$ DIR EXAMPLE

```

\$ chiral example
**** Generating CHIRAL input file
**** (Note: User input may be required here)
**** Executing CONCHI
**** (Note: NO user input expected here)
STRUCTURE NAME
**** Executing CHIRAL
**** (Note: User input may be required here)
STRUCTURE NAME -example
EVALUATE ATOM 2 TYPE C (Y OR N) Y
** R/S ** 2 C R 1
FINISHED
\$

\$ LOOP EXAMPLE
**** Generating loop input file
**** (Note: User input may be required here)
**** Executing CONLGP
**** (Note: No user input expected here)
STRUCTURE NAME -
**** Executing LOOP
**** (Note: No user input expected here)
STRUCTURE -
PRINTOUT SWITCH [0]

THE CALC LOG P IN OCT/H20 IS << 0 130 >>

\$

```

$ TYPE EXAMPLE CON
10example
C 1 0.699363 0.292916 1 311681 1 2 5 3 4 9 10
C 2 0.000000 0.000000 0.000000 0.000000 22 1 1 3 4 8
C 3 1.511236 0.000000 0.000000 0.000000 22 2 2 4 9 10
O 4 0.758611 1.296481 0.000000 0.000000 38 2 2 4 9 10
H 5 -0.969636 1.372084 1.363806 0.000000 5 1 1 3 4 9
H 6 -0.057124 0.042649 2.186275 0.000000 5 1 1 3 4 9
H 7 1.630848 0.313295 1.383057 0.000000 5 1 1 3 4 9
H 8 -0.556236 0.143610 0.924110 0.000000 5 2 2 4 9 10
H 9 2.040805 0.176094 0.932194 0.000000 5 3 3 4 9 10
H 10 2.060560 0.165014 0.922650 0.000000 5 3 3 4 9 10

```

```

$ CONEDIT EXAMPLE
**** Executing CONEDIT
**** [Note: User input may be required here]
STRUCTURE NAME = EXAMPLE
CMD >HELP
ALLOWED COMMANDS ARE
JOIN INVERT HELP CHANGE END ADD BREAK EXAMINE
JOIN ASKS FOR TWO ATOM NUMBERS TO BOND TOGETHER
INVERT ASKS FOR TWO ATOMS WHOSE COORDINATES TO SWAP
HELP PRINTS THIS TEXT
CHANGE LETS YOU CHANGE ATOM-TYPES, COORDINATES, OR THE TITLE LINE
END TERMINATES EXECUTION (EQUIVALENT TO CTRL Z)
ADD LETS YOU ADD ATOMS AND LONE PAIRS
BREAK DISCONNECTS THE ENDS OF A BOND AND FILLS OUT VALENCE WITH HYDROGENS
EXAMINE TELS THE ENVIRONMENT OF AN ATOM
CMD >CHANGE
CHG >TYPE
ATOM NUMBER = 5
NEW SYMBOL(2 SPACES, RIGHT JUSTIFIED) = C
CHG >
CMD >JOIN
I,J = 1,5
CMD >
NEW STRUCTURE NAME [EXAMPLE] NEWEXAMPLE
Change to structure [EXAMPLE]

```

```

$ TYPE NEWEXAMPLE.CON
10example
C 1 -0.699363 0.292916 1 311681 1 2 5 3 4 9 10
C 2 0.000000 0.000000 0.000000 0.000000 22 1 1 3 4 8
C 3 1.511236 0.000000 0.000000 0.000000 22 2 2 4 9 10
O 4 0.758611 1.296481 0.000000 0.000000 38 2 2 4 9 10
H 5 -0.969636 1.372084 1.363806 0.000000 5 1 1 3 4 9
H 6 -0.057124 0.042649 2.186275 0.000000 5 1 1 3 4 9
H 7 1.630848 0.313295 1.383057 0.000000 5 1 1 3 4 9
H 8 -0.556236 0.143610 0.924110 0.000000 5 2 2 4 9 10
H 9 2.040805 0.176094 0.932194 0.000000 5 3 3 4 9 10
H 10 2.060560 0.165014 0.922650 0.000000 5 3 3 4 9 10

```

\$ drvplot example
**** Executing DRVPLAT
**** (Note: User input may be required here)
Enter structure name # 1
example
Enter structure name # 2

7

9	8	7	6	5	4	3	2	1
ALL	TORSION	OTHER	VAND 1,4	STR BEND	BENDING	COMPRESS	TOTAL E	EXIT

9

ALL

8

TORSION

7

OTHER

6

VAND J.4

5

STR BEND

4

BENDING

3

COMPRESS

2

TOTAL

1

EXIT

```

$ conami example
*** Executing CONAMI
*** (Note: User input may be required here)
Structure Name [quit] example
Are Cartesian Coordinates desired (Y/N) [Y]
Ampac options [T-30M] SCF XYZ AM1 MOPLOT
$
$ ampac example
*** Executing AMPAC
INTERACTIVE or BATCH [BATCH]
Job EXAMPLE (queue $SYS$BATCH, entry 1/00) started on $SYS$BATCH
$
$
Batch queue $SYS$BATCH
$
Type example are

```

SUMMARY OF AM1 CALCULATION

VERSION 1.00

5 APR 87 C(3) H(6) O(1)

ISCF WAS SPECIFIED, SO FLETCHER POWELL WAS NOT USED
SCF FIELD WAS ACHIEVED

```

HEAT OF FORMATION      11 010825 KCAL
ELECTRONIC ENERGY     2387 380332 EV
CORE-CORE REPULSION    1601 607818 EV
DIPOLE                  2 14527 DEBYE
NO. OF FILLED LEVELS   12
IONISATION POTENTIAL   11 306115 EV
MOLECULAR WEIGHT       58.080
SCF CALCULATIONS      1
COMPUTATION TIME       11 88 SECONDS

```

FINAL GEOMETRY OBTAINED

```

T-30M SCF XYZ AM1 MOPLOT
example
C 0 000000 0 0 000000 0 0 000000 0 0 000000 0 0 000000 0 0 000000
C 1 515062 1 0 000000 0 0 000000 0 1 0 0 0
C 1 511236 1 117 490831 1 0 000000 0 2 1 0 0
O 1 499102 1 59 864254 1 257 411627 1 3 2 1 0
H 1 113718 1 109 869511 1 264 098016 1 1 2 3 3
H 1 113562 1 111 733575 1 24 859862 1 1 2 3 3
H 1 113666 1 109 654174 1 144 623228 1 1 2 3 3
H 1 088118 1 118 280065 1 159 117824 1 2 1 3
H 1 086480 1 319 170975 1 156 714357 1 3 2 1 1
H 1 086402 1 120 373578 1 357 551633 1 3 2 1 1
O 0 000000 0 0 000000 0 0 000000 0 0 0 0 0

```

CHARGE

C(3) H(6) O(1)

```

0 2080
0 0421
0 0927
-0 2962
0 0847
0 0906
0 0902
0 1162
0 1164
0 1209

```

```

$ denscomp example
First MO to be plotted | 1 | 12
Last MO to be plotted | 12 | 12
Contour level | 0.08 | :
**** Executing DENSComp
INTERACTIVE or BATCH | BATCH | :
Job EXAMPLE (queue SYS$BATCH, entry 1/0/) started on SYS$BATCH
$
q
Batch queue SYS$BATCH
term pdf
~~~~~$
densplot example
First MO to be plotted | 1 | 4 | 12
Last MO to be plotted | 12 | :
Cubic Spline (C) or Least Squares (L) | C | :
Orientation angles, and scale | 45,45,1 0 | 0.0,0,1 0
Plot title | EXAMPLE, M O s 12 to 12 |
**** Executing DENSPLot
INTERACTIVE or BATCH | BATCH | :
Job EXAMPLE (queue SYS$BATCH, entry 1/0B) started on SYS$BATCH
$

```

\$ term 4014

\$ replot example

After you have been prompted for the required data,
you may have to type a character to start the
generation of the plot

Plot type (BLX DEN MO VWX *other*) | *other* | den

First MO to be plotted | 1 | 12

Last MO to be plotted | 12 | 12

**** Executing REPILOT

**** (Note: User input may be required here)

**** (This program pauses after every page. Type any character to continue)

**** (A character of input is sometimes required to begin the display)

EXAMPLE. M.O. 12 to 12

EXAMPLE. M.O.s 13 to 13

```

$ conmerge example
**** Executing CONMERGE
**** (Note: User input may be required here)

THE OUTPUT STRUCTURE WILL NOW BE CREATED FROM THE
INPUT STRUCTURE(S), ALONG WITH REQUESTED ORIENTATION INFO
SOME REQUESTED ORIENTATION INFO IS FLAGGED WITH ****
*
FLAGGED INPUT ACCEPTS 1 OR 2 ENTRIES FOR REFERENCES
1 ENTRY(1)-USE ATOM 1
2 ENTRIES(1 J)-USE 1,J MIDPOINT

STRUCTURE NAME - example
ORIGIN ATOM ***** 2
ATOM ALONG AXIS 1 ***** 3
AXIS (1-X,2-Y,3-Z) [1]
ATOM FOR AXIS 1 AXIS 2 PLANE ***** 4
AXIS 12 - 2
TRANSLATION ORIGIN (0 IF NONE)[0] - *****
ARE ANY INTERNAL ROTATIONS TO BE DONE (Y OR N) n

COORDINATES TRANSLATED TO PLACE ATOM 2 AT ORIGIN
MOLECULE ROTATED TO PLACE ATOM 3 ALONG X AXIS
MOLECULE ROTATED TO PLACE ATOM 4 IN X Y PLANE

ORIENTED COORDINATES
ATOM X Y Z
( 1) 0.69936 0.29292 1.31168 ( 0)
( 2) 0.00000 0.00000 0.00000 ( 0)
( 3) 1.51124 0.00000 0.00000 ( 0)
( 4) 0.75861 1.29648 0.00000 ( 0)
( 5) 0.96964 1.37208 1.36381 ( 0)
( 6) 0.05712 0.04265 2.18628 ( 0)
( 7) 1.63095 0.31129 1.38306 ( 0)
( 8) 0.58624 0.14361 0.42411 ( 0)
( 9) 2.04080 0.17609 0.93219 ( 0)
(10) 2.06056 0.16501 0.92265 ( 0)

STRUCTURE NAME ***** 2
ORIGIN ATOM ***** 2
ATOM ALONG AXIS 1 ***** 3
AXIS (1-X,2-Y,3-Z) [1]
ATOM FOR AXIS 1 AXIS 2 PLANE ***** 4
AXIS 12 - 2
TRANSLATION ORIGIN (0 IF NONE)[0] *****
ARE ANY INTERNAL ROTATIONS TO BE DONE (Y OR N)

```

COORDINATES TRANSLATED TO PLACE ATOM 2 AT ORIGIN
 MOLECULE ROTATED TO PLACE ATOM 3 ALONG X AXIS
 MOLECULE ROTATED TO PLACE ATOM 4 IN X Y PLANE

ORIENTED COORDINATES

ATOM	X	Y	Z
(1)	0.69936	0.29292	1.11168
(2)	0.00000	0.00000	0.00000
(3)	1.51124	0.00000	0.00000
(4)	0.75861	1.29644	0.00000
(5)	0.96964	1.37208	1.16181
(6)	-0.05712	0.04265	2.18628
(7)	1.63085	0.91329	1.18106
(8)	0.55624	0.14361	0.92411
(9)	2.04080	0.17609	0.93219
(10)	2.06056	0.16501	0.92265

STRUCTURE NAME
 ENTER TITLE FOR COMBINED FILE

example

superimpose example
 OUTPUT STRUCTURE NAME

{ mirror exmerge

\$ pluto exmerge
 **** Generating pluto input file

**** (Note: User input may be required here)

**** Executing COMPLD

**** (Note: No user input expected here)

STRUCTURE NAME

((1) H(

1. exmerge

PLUTO

SUPERIMPOSE EXAMPLE

\$ CONAMI EXAMPLE
*** Executing CONAMI
*** (Note: User input may be required here)
Structure Name | quit* | EXAMPLE
Are Cartesian coordinates desired (Y/N) | Y | N
Ampac options | T-10M AMI MOPLAD |
Any parameters to optimize (Y/N) | N | N |
Specify a reaction coordinates (Y/N) | N |
\$ DRAW EXAMPLE

DRAW. PLOTS MOLECULAR GEOMETRIES
V 1 0

What is name of file [AMI] EXAMPLE

EXAMPLE AMI

NO	AT	X	Y	Z
4	C	3 142	-0 068	4 320
5	C	4 358	-0 082	5 444
6	H	2 782	1 031	4 303
7	H	2 614	0 767	4 433
8	H	3 864	0 059	3 345
9	C	3 957	0 553	6 755
10	O	4 866	1 283	5 812
11	H	5 161	-0 816	5 404
12	H	4 460	0 246	7 668
13	H	2 988	1 034	6 859

IRAW> DISPLAY
DRAW> DISPLAY> NAG
NAG>YA
DRAW> DISPLAY> QUIT

EXAMPLE AMI

NO	AT	X	Y	Z
4	C	3.342	-0.068	4.320
5	C	4.358	-0.082	5.444
6	H	2.782	-1.031	4.303
7	H	2.614	0.767	4.433
8	H	3.864	0.059	3.345
9	C	3.957	0.553	6.755
10	O	4.866	1.283	5.812
11	H	5.161	-0.816	5.404
12	H	4.460	0.246	7.668
13	H	2.988	1.034	6.859

DRAW DISPLAY ONWARD
 DRAW DISPLAYS ONWARD
 NO TORQUE DISPLAY AND COORDINATES WITH FLOW
 DRAW DISPLAY ORTER
 ORTER DISPLAY QUIT

DRAMA

STRUCTURE NAME

```

$ bulkcomp example
VDI input file does not exist Make it? ( Y )
**** Generating BULKCOMP input file
**** (Note: User input may be required here)
**** Executing CONVDI
**** (Note: User input may be required here)
OUTPUT STRUCTURE NAME = example
STRUCTURE NAME = example
ORIGIN ATOM = 2
ATOM ALONG AXIS 1 = 3
AXIS (1 = X, 2 = Y, 3 = Z) (1) =
ATOM FOR AXIS 1 = AXIS 2 PLANE = 4
AXIS #2 = 2
TRANSLATION ORIGIN (0 IF NONE) (0) =
ARE ANY INTERNAL ROTATIONS TO BE DONE (Y OR N)
INCLUSION FACTOR (1.0) =

```

COORDINATES TRANSLATED TO PLACE ATOM 2 AT ORIGIN
 MOLECULE ROTATED TO PLACE ATOM 3 ALONG X AXIS
 MOLECULE ROTATED TO PLACE ATOM 4 IN X Y PLANE

ORIENTED COORDINATES

ATOM	X	Y	Z
(1)	0.69936	0.29292	1.31168
(2)	0.00000	0.00000	0.00000
(3)	1.51124	0.00000	0.00000
(4)	0.75861	1.29648	0.00000
(5)	-0.96964	-1.37208	1.36381
(6)	-0.05712	-0.04265	2.18628
(7)	1.63085	0.31330	1.38306
(8)	0.55624	0.14361	-0.92411
(9)	-2.04081	0.17609	-0.91219
(10)	2.06056	0.16501	0.92265

```

STRUCTURE NAME
ORIGIN ATOM = 2
ATOM ALONG AXIS 1 = 3
AXIS (1 = X, 2 = Y, 3 = Z) (1) =
ATOM FOR AXIS 1 = AXIS 2 PLANE = 4
AXIS #2 = 2
TRANSLATION ORIGIN (0 IF NONE) (0) =
ARE ANY INTERNAL ROTATIONS TO BE DONE (Y OR N)
INCLUSION FACTOR (1.0) =

```

COORDINATES TRANSLATED TO PLACE ATOM 2 AT ORIGIN
 MOLECULE ROTATED TO PLACE ATOM 3 ALONG X AXIS
 MOLECULE ROTATED TO PLACE ATOM 4 IN X Y PLANE

ORIENTED COORDINATES

ATOM	X	Y	Z
(1)	0.69936	0.29292	1.31168
(2)	0.00000	0.00000	0.00000
(3)	1.51124	0.00000	0.00000
(4)	0.75861	1.29648	0.00000
(5)	-0.96964	1.37208	1.36381
(6)	-0.05712	-0.04265	2.18628
(7)	1.63085	0.31330	1.38306
(8)	0.55624	0.14361	-0.92411
(9)	-2.04081	0.17609	-0.91219
(10)	2.06056	0.16501	0.92265

D

ENTER TITLE FOR COMBINED FILE (75 CHAR MAX.)

Probe Epsilon? [0.075]

Probe Radius? [1.50]

Contour Level? [0.5]

*** Executing BULKCOMP

INTERACTIVE OF BATCH [HATCH]

Job EXAMPLE (queue SYSSRATCH, entry 1946) started on SYSSBATCH

\$

EXAMPLE, Common Volumes Plot

APPENDIX B

Tricothecene Derivative Geometries

16 (active antileukemic)**Interatomic Distance Matrix (Å)**

		8	15	18	23
ether O	8				
epoxide	15	3.7			
ketone	18	4.9	6.5		
ketone	23	3.3	3.8	7.8	
hydroxyl	38	4.4	3.0	7.4	2.9

17 (active antileukemic)**Interatomic Distance Matrix (Å)**

		8	15	17	22
ROR	8				
epoxide	15	3.7			
-OH	17	2.9	4.5		
-OCOR	22	4.4	3.0	6.3	
epoxide	61	2.5	5.9	2.7	6.7

18 (inactive antileukemic)**Interatomic Distance Matrix (Å)**

		8	15	22
ROR	8			
epoxide	15	3.7		
-OCOR	22	4.4	3.0	
epoxide	58	3.7	6.7	6.5

19 (Inactive antileukemic)**Interatomic Distance Matrix (Å)**

		8	15	18
ROR	8			
epoxide	15	3.7		
C=O	18	4.9	6.5	
-OCOR	38	4.4	3.1	7.4

20 (active - protein synthesis inhibition)**Interatomic Distance Matrix (Å)**

		8	15	19
ROR	8			
epoxide	15	3.7		
-OH	19	2.8	4.4	
-OCOR	37	4.4	3.0	3.4

21 (active - protein synthesis inhibition)**Interatomic Distance Matrix (Å)**

		16	29
ROR	16		
epoxide	29	3.7	
OH	34	4.4	3.0

22 (active - protein synthesis inhibition)**Interatomic Distance Matrix (Å)**

	8	15
ROR	8	
epoxide	15	3.7
-OAc	21	2.8
		4.4

23 (inactive - protein synthesis inhibition)**Interatomic Distance Matrix (Å)**

		8	15
ROR	8		
epoxide	15	3.7	
-OAc	19	2.8	4.4

24 (inactive - protein synthesis inhibition)**Interatomic Distance Matrix (Å)**

		16	29
ROR	16		
epoxide	29	3.7	
-OH	36	3.9	4.3

25 (Inactive - protein synthesis inhibition)**Interatomic Distance Matrix (Å)**

		15	28
RQR	15		
epoxide	28	3.7	
-OH	33	4.4	3.1

Appendix C

Investigations into the Synthesis of Cyclobenzazaundecines

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N-(2-bromo-3,4-dimethoxybenzyl)-N-tosyl-3-bromo-4-methoxy-phenethylamine (28) from 27 C 45

Attempted synthesis of

1,2,12-trimethoxy-5,6,7,8-tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28 C 47

Attempted synthesis of

1,2,12-trimethoxy-5,6,7,8-tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28 C 47

Attempted synthesis of

1,2,12-trimethoxy-5,6,7,8-tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28 C 47

Attempted synthesis of

1,2,12-trimethoxy-5,6,7,8-tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28 C 48

Attempted synthesis of

1,2,12-trimethoxy-5,6,7,8-tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28 C 48

Attempted synthesis of

1,2,12-trimethoxy-5,6,7,8-tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28 C 49

Attempted synthesis of 1,2,12-trimethoxy-5,6,7,8-

tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28 C 49

Attempted synthesis of 1,2,12-trimethoxy-5,6,7,8-

tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28 C 51

References **C 52**

INTRODUCTION

The search for new classes of anti-cancer drugs has taken researchers along two main routes. The extraction of materials from natural sources (mostly plants) for medicinal purposes has been practiced since the beginning of recorded history, and is still the primary source of new bioactive compounds. In the last century it has become common to investigate synthetic derivatives of known active compounds, and even materials which are structurally related but not derived from natural materials

Amyrillidaceae Alkaloids

The alkaloids are a family of over two thousand nitrogen-containing natural products found in approximately forty plant families. The lycorine alkaloids (eg. lycorine (1)) are pyrrolophenanthridines which are found in the family *Amaryllidaceae*. It has been proposed¹ that they are biosynthesized from norbelladine (2) via a free radical coupling of the phenols in an ortho,para

sense (scheme 1), while the other *Amaryllidaceae* are the result of a similar coupling, but through differing orientations of the phenols.

The *Amaryllidaceae* family of alkaloids contain a number of structurally

Scheme 1
The Biosynthesis of Norbelladine

related compounds possessing potentially useful biological activity. Lycorine

(1) and hemanthamine (3) possess KB tissue culture inhibitory activity², and the latter is active³ against sarcoma 37. Pretazettine (4) is active against

advanced Rauscher leukemia in mice⁴. Pretazettine and pseudolycorine (5) inhibit protein synthesis in tumour cells⁵, and the latter has antiviral activity

against leukemia virus and neurotropic RNA virus⁶. Narciclasine (6) has been

shown to have antitumor effect and antimitotic activity⁷. Most of these compounds, including dihydrolycorine (7), inhibit HeLa cell growth⁸ by inhibiting peptide bond formation. Ungeremine (8) and its hydrochloride salt have been reported to have inhibitory activity against a wide variety of tumors², as well as leukemia P388.

Lycoranes are structurally similar to other well-known anti-cancer compounds, namely podophyllotoxone⁹ (9), steganacin¹⁰ (10a) and steganangin (10b).

3 of/de 3

Synthetic Approaches

Phenol couplings

There are two broad classes of phenol couplings, internal and external¹¹. Internal, or non-oxidative coupling, involves an internal oxidation-reduction with no net overall oxidation during the coupling step. External coupling involves the transfer of electrons to an external oxidizing agent. This process may involve radical or non-radical reaction intermediates. As well, radical couplings may proceed by either two electron or one electron pathways. Two electron oxidants, such as lead tetraacetate, benzoyl peroxide, and alkaline persulphate, form free radicals as intermediates, but ultimately the reactive species is cationic. One electron radical couplings may involve homolytic aromatic substitution, or the direct coupling of aryloxy radicals.

Theoretical Studies

It is well known from ESR studies¹² that the spin density of phenoxyl radicals is twice as high at the para position than at the ortho. Furthermore, frontier orbital theory predicts that the coupling of delocalized radicals would

occur at the site of highest spin density¹³. The oxidative coupling of phenols was studied extensively by Armstrong et al¹⁴, who found that the orientation of

Possible modes of phenolic coupling

Scheme 2

the coupling is determined primarily not by spin density factors, but by steric ones. They determined that coupling occurs with the aromatics in a stacked orientation (scheme 2), with the phenols eclipsed only in the absence of ortho

or para methyl groups; in the presence of such a group, the aryl rings stack such that the interactions between the methyls are minimized, but still allow overlap of the spin dense ortho and para positions. This results in o,p coupled materials, and in more hindered systems, the o,o products. Analogous results were obtained with different substitution patterns, using the same criteria. Other factors, such as solvent, temperature, and oxidant play a role; higher temperatures favour o,o products, while metal oxidants in aqueous solvents tend to favour p,p coupled products. The tendencies of intermolecular coupling of phenols do not necessarily apply to the intramolecular cyclizations of norbelladine derivatives, where strain energy may prevent the formation of certain reactive intermediates. All of the naturally occurring *Amaryllidaceae*

11

alkaloids are the result of p,p or o,p coupling. In our laboratory, ApSimon and Dixit¹⁵ obtained reasonable yields of o,o coupled norbelladine analogues by

anchoring the nitrogen to a styrene-divinylbenzene copolymer modified with a succinoyl side chain, using VOCl_3 as the oxidant. The orientation of the reactive intermediate may have been due to a steric constraint of the polymer, or to the formation of a highly strained vanadyl complex (11), or both.

Metal Catalyzed Aryl Couplings

The Ullmann Reaction, and variations

The coupling of aryl halides in the presence of copper is known as the Ullmann reaction (see reviews by Fanta¹⁶⁻¹⁸). For years this reaction was of limited synthetic use, since the rather severe experimental conditions resulted in large amounts of decomposed and polymerized products. The introduction of DMF as a solvent, and the discovery of methods to activate the metallic copper (such as chemical or electrolytic precipitation), expanded the useful range of this reaction. However, it wasn't until the substitution of other metals for copper that the coupling of aryl halides became a reaction which could be performed under extremely mild conditions and with high yields.

The coupling of aryl halides with nickel was first discovered by Semmelhack et al¹⁹, who coupled a variety of substrates with bis(1,5-cyclooctadiene)nickel. DMF was found to be the only suitable solvent, and the presence of nitro groups on the substrate retards reactivity completely. Like traditional Ullmann reactions, groups ortho to the halides slows (and in this case, eliminates) reaction. High temperatures are also incompatible with this reaction, causing decomposition of the nickel reagent.

Later, Semmelhack and co-workers²⁰ improved on their earlier work by introducing $\text{Ni}(\text{PPh}_3)_4$ as a coupling reagent. Again using DMF as solvent, this group was able to perform intramolecular couplings, synthesizing cyclic compounds with a range of ring sizes. The yields of dibenzoalkanes was about 80%, for ring sizes up to nine; the dibenzodecane was produced only in 40% yield.

At approximately the same time, Kende and co-workers²¹ published a simple method for the in-situ generation of $\text{Ni}(\text{PPh}_3)_4$ by the reduction of $\text{NiCl}_2(\text{PPh}_3)_2$ with zinc powder in DMF, in the presence of PPh_3 . Many aryl halides were shown to couple, but substrates with two ortho groups did not. These workers did not show the applicability of this method to mixed couplings.

A further improvement of this method was demonstrated by Kumada and co-workers²², namely the generation of $\text{Ni}(\text{PPh}_3)_4$ under the same conditions as Kende, but using a catalytic amount of nickel, and a small amount of PPh_3 relative to the substrate. The coupling reaction can be enhanced by the presence of iodide ion, allowing higher yields at lower reaction temperatures. Again, the scope of the reaction was limited to the homo coupling of unhindered aryl bromides. Ortho groups, or other solvents (EtOH, MeCN, THF) resulted in greatly reduced yields.

The next logical step in the evolution of nickel catalyzed couplings was prompted by the finding that Ni^0 , generated directly from Ni^{II} salts by reduction with Zn powder²³, catalyze the coupling of aryl halides in the presence of iodide ion in HMPA without the necessity of phosphine ligands. These workers found that the presence of various phosphines, or performing the reaction in less polar solvents (even DMF!), gave only Finklestein products (ie. aryl iodides) with aryl halides. The authors claim that this approach was successful in the coupling of aryl halides containing ortho withdrawing groups; however, their own tables show a wide range of yields for identical reactions, with only very minor changes in condition.

Using a very closely related method, Rieke and co-workers²⁴ coupled aryl halides using activated nickel metal, generated from Ni^{II} halides by reduction with lithium metal in glyme using naphthalene as an electron carrier. Aryl iodides coupled better than bromides (which tended to dehalogenate), although this can be overcome to some extent by generating the nickel from the iodide salt; presumably some exchange occurs with the resulting iodide ion in solution, as suggested by previous studies. Ortho groups, especially electron withdrawing ones, slow the reaction considerably. In contrast, withdrawing groups at other positions slowed the reaction less than donating ones. The authors did not try to explain this behaviour. This work complemented earlier work²⁵ by the principal author which demonstrated the usefulness of similarly prepared copper metal in the classical Ullmann reaction.

The mechanism of nickel catalyzed coupling has been postulated by several authors. Semmelhack et al¹⁹ suggested that the coupling using bis(1,5-cyclooctadiene)-nickel(0) occurred according to scheme 3.

(L = solvent or COD)

SCHEME 3. Bis(1,5-cyclooctadiene)-nickel(0) aryl halide coupling

This scheme essentially involves two successive oxidative additions of an aryl halide to the nickel, followed by reductive elimination of the biaryl moiety.

In a very extensive study, Tsou and Kochi²⁵ concluded that aryl coupling proceeds by the following radical chain process.

SCHEME 4. Free radical mechanism for Nickel catalyzed aryl halide coupling.

Their studies, however, were all performed in benzene, and did not necessarily correspond to product studies done in other solvent systems (such as DMF²⁶).

Riecke and co-workers²⁴ presented a mechanism similar to that in scheme 3. Using iodopentafluorobenzene as substrate, they were able to trap bis(triphenylphosphine)-bis(pentafluorophenyl)nickel; and so they proposed a disproportionation reaction as the means of producing the intermediate that undergoes reductive elimination.

(L = solvent)

Scheme 5. Mechanism for aryl halide coupling using Riecke's nickel

Transition Metal Catalyzed Grignard Reactions

Since the early 1940's it has been known that it is possible to couple Grignard reagents with aryl halides to form biaryls. In his pioneering work, Kharasch²⁷ coupled phenyl magnesium bromide and bromobenzene in the presence of cobalt chloride. Twenty years later, Morizur²⁸ extended this work to include uranium salts, and some organolithium compounds instead of organomagnesiums. Yields were moderate for most substrates (50-60%).

Although a large volume of literature has been published on the coupling of aryl Grignards with alkyl halides (see the review by Felkin and Swierczewski²⁹ and references cited, and other references³⁰⁻³⁸), relatively little new work has been released on aryl-aryl coupling using catalysts which are useful for Ullmann types of reactions (such as nickel and palladium).

The diarylation of 1,8-diiodonaphthalene with aryl Grignards was the first example of the use of nickel in a Kharasch coupling of aromatics³⁹. Two catalysts, $\text{Ni}(\text{acac})_2$ and dichloro[1,2-bis(diphenylphosphino)ethane]nickel(II) were found to be effective, though the former was investigated more extensively due to its ready availability. The reaction only occurs in reasonable yields in the presence of at least seven equivalents of Grignard reagent. Some

homo coupling of the Grignard reagent was observed. Aryl bromides have nearly the reactivity of the corresponding iodide, but the iodo-Grignards have much greater reactivity than the corresponding bromide. This difference in reactivity was not evident in less hindered substrates (ie. not peri-dihalo naphthalenes).

Tamao and co-workers⁴⁰ performed the first methodical investigation of the scope of the nickel-phosphine catalyzed Grignard reaction. Their study clearly showed the superior catalytic activity of nickel bearing a bidentate phosphine ligand, especially where the spacer chain is three carbons long. There are two exceptions to this rule. First, allylic and vinylic Grignard reagents were best reacted in the presence of a bidentate phosphine bearing only alkyl substituents. Secondly, hindered Grignards reacted best in the presence of unidentate ligands. Generally, triphenylphosphine is the only active unidentate ligand, and analogous complexes of Pd (such as PdX_2L_2 or Co) were inactive. Selected catalysts were shown to be very resistant to aging, having essentially unchanged activity after 16 hours in solution in the presence of alkyl halides. The relative reactivity of aryl halides (with an alkyl halide) does not always follow the expected order (ie. $\text{I} > \text{Br} > \text{Cl} > \text{F}$), this effect being dependant on the catalyst used in the competition experiment; chlorobenzene was

occasionally more reactive than bromobenzene. In fact, the high reactivity of aryl chlorides is one of the remarkable findings of the study. Even fluorobenzene is a moderate substrate. Diethyl ether proved to be a better solvent than THF, which the authors attributed to the higher solvent shell interaction on nickel by the more basic THF. The mechanism of the reaction is as follows:

"Induction" Phase

"Propagation" Phase

SCHEME 6. Kharasch coupling using bidentate phosphine ligands

Tamao et al⁴¹ later showed the usefulness of these catalysts in the coupling of nitrogen and sulphur heterocycles.

A method to couple aryl boronic acids with aryl halides was devised by Suzuki and co-workers⁴². In the presence of $\text{Pd}(\text{PPh}_3)_4$, refluxing in a two-phase benzene / 2M aq. Na_2CO_3 solution, the reactants couple in moderate yield. Hindered substrates couple slowly, but the reaction could be improved by performing the reaction in refluxing toluene.

The cross-coupling of Grignard reagents with 2-halogenobenzothiazoles was shown to be catalyzed by a variety of nickel reagents⁴³. The authors determined that the ideal ratio of phosphine ligand to nickel is approximately 1.0, and introduced the new catalyst $\text{NiBr}_2(\text{DMSO})(\text{PMe}_3)$. They proposed the following mechanism for the reaction:

"Induction"

"Propagation"

SCHEME 7. Kharasch coupling using $\text{NiBr}_2(\text{DMSO})(\text{PMe}_3)$

Based on this mechanism, the authors proposed that the key step in the reaction is the loss of a phosphine ligand and the formation of the co-ordinated species. They argued that smaller ligands (such as PMe_3) increase the ease with which the benzothiazole coordinates with the nickel, while those of lower basicity are more easily displaced. They also found that the order of reactivity

of the halobenzothiazoles is $F > Cl > I$, which further supports their steric argument:

RESULTS AND DISCUSSION

Tyramine Chemistry

Three important ideas were paramount in the functionalization of tyramine for the desired synthesis.

1) The site of coupling to the other aromatic ring had to be activated, or marked, in some way. Since the chemistry of phenol couplings had been extensively investigated, and had not produced yields desirable for a multi-step synthesis, the condensation of aryl halides using an Ullmann strategy or a Kharasch type of process was a good alternative (eg. scheme 8). Some halogen, then, had to be introduced ortho to the phenolic site.

2) The target compound possessed three aromatic methyl ethers, one of which would arise from the tyramine phenol. In view of the sometimes unreliable chemistry of phenols it would be good to protect the phenol early in the synthetic sequence. Formation of the methyl ether fulfills the ultimate

Intermolecular Aryl coupling

Scheme 8

structural requirement, and conveniently offers a protecting group which is easily formed and stable under a variety of conditions.

3) The amine, which will later form part of the heterocyclic ring, is incompatible with a number of reagents, possesses questionable stability with regard to routine storage of the material, and can cause difficulty in the isolation and purification of the desired materials. This is further compounded

in the presence of a free phenol, where amphoterism puts constraints on the pH under which the material can be worked with conveniently.

It was decided to protect the amine as its acetamide derivative. This group has relatively high chemical stability (compatible with Grignard conditions, high and low pH) while its removal can be accomplished in refluxing aqueous HCl, which will not cleave aryl methyl ethers. Reaction of tyramine hydrochloride with acetic anhydride in the presence of several weak bases (NaOAc, Et₃N, pyridine) did not give satisfactory yields of product. A method was found⁴⁴ that allows the selective amidation of tyramine by acetyl exchange with isopropenyl acetate in refluxing DME. High yields of pure 15 were obtained, with no evidence of acetylation of the phenol.

The bromination of 15 was accomplished using the standard conditions of bromine in acetic acid. Initially, the highly crystalline solid 16 was incorrectly identified as the dibromo compound 17. The aromatic dibromination of phenols is a common problem, while the facile formation of hydrobromide salts of amides is rare. The hydrogen bonding of two molecules of phenol to dimethylacetamide has been documented⁴⁵, and, in retrospect, it is possible that we obtained a material with one molecule of HBr and one tyramine phenol (inter- or intra-molecularly) bonded to the amide. The monobromination with

15

16

17

18

19

20

NBS in DMF⁴⁶ was also attempted, but no reaction was observed. It was therefore temporarily decided to pursue an alternative route.

N-acetyl tyramine was O-methylated with MeI in acetone in the presence of K_2CO_3 . The halogenation of this non-phenolic product (18) was investigated according to methods used for compounds not normally considered as being "activated" towards aromatic halogenation. The use of $Br_2 / AlBr_3$ was

impossible due to the great likelihood of cleavage of the amide or aromatic methyl ether. Milder Lewis acids, such as copper chloride or bromide, were ineffective. Similarly useless was the strategy of lithiation-halogenation. Reaction of 18 with 2 equivalents of nBuLi followed by quenching with NBS did not give the desired product 12, nor the isomer 19, possible via ortho-activation by the amide (20).

Re-examination of compound 16 revealed the previous success of the bromination under standard conditions. Methylation with MeI / K₂CO₃ / acetone afforded the desired product 12 in good yield.

Preparation of the 3,4-dimethoxy-benzoic acid moiety

The metallation of the 2-position of amides of 3,4-dimethoxy-benzoic (veratric) acid (13) has been extensively studied by Sniekus and co-workers⁴⁷. Introduction of lithium or magnesium at this position would allow a Kharasch process; a bromine or iodine would permit an attempt at an Ullmann reaction.

Veratric acid was functionalized to the amide 13 ($Y = H$) by reaction with thionyl chloride, followed by diethyl amine. This amide was lithiated with $s\text{-BuLi}$ in THF in the presence of TMEDA, and the reaction quenched with a number of halogenating agents (Br_2 , NCS, NBS). All attempts failed to produce any new products. These results are in accord with Sniekus' work (although he tried the reaction only with molecular bromine); his solution was to activate the lithiation site by silylation, followed by ipso-bromination.

Although the silylation was successful, ipso-bromination failed to give any of the desired aryl halide. These results eliminated the possibility of an Ullmann process. Although the successful coupling of lithio-aromatics with aryl halides has been seldom documented in the literature, the reaction of the 2-lithio diethyl veratramide with the functionalized tyramine moiety was attempted, as several steps could be saved. The reaction failed, however, forming only insoluble materials. Alternately, the exchange of lithium with magnesium was tried by adding MgBr_2 etherate to the lithiated amide in diethyl ether or DME. This strategy was also unsuccessful, resulting in unchanged starting materials.

In view of the reluctance of the tyramine and veratramide moieties to react in a Kharasch sense, an alternate synthesis was undertaken which would

use the intramolecular Ullmann reaction to couple the aromatic portions of the molecule. In this approach, the aromatics would be joined first by a side chain (which later becomes the non-aromatic portion of the target's cycloundecine ring). Under high dilution, this dihalide would have a greater chance of coupling intramolecularly, thereby reducing the risk of homo-coupling of the more reactive halide. In this case, the tyramine moiety is probably more reactive, due to the presence of only one ortho group.

Isovanillin Chemistry

The isovanillin fragment was functionalized in a predictable and straightforward manner (scheme 9). Bromination was accomplished with molecular bromine in acetic acid; the product 22, which conveniently crystallizes out of solution, contains none of the undesired para-brominated isomer. The phenol was methylated with MeI in the presence of K_2CO_3 in acetone, giving compound 23 in good yield.

Isovanillin functionalization

Scheme 9

Formation of the precursor dibromide

The linking of isovannilin derivative 23 with tyramine (24) was done in an identical manner to that used by ApSimon and Dixit¹⁵. The imine was formed on refluxing the two materials in dry ethanol (scheme 10), and was reduced in situ by addition of NaBH_4 . The isolated yield of 25 was only moderate. As the molecule possesses both an acidic phenol and a basic amine, the reaction was adjusted to pH 9 (as previously described in ref. 15) to allow the extraction with EtOAc ; this may not be that close to the isoelectric point and so some material may have been lost in the aqueous layer. As well, the neutral molecule may have some water solubility.

The preparation of the tyramine portion of **25** for intramolecular coupling (scheme 10) was similar to that done previously. Again, the phenol was easily

Scheme 10

brominated using Br₂ in acetic acid, giving the hydrobromide salt of 26. This product could not be directly methylated due to the presence of the amine, which would complicate the synthesis by the formation of tetraalkyl ammonium salts. The amine was therefore protected by tosylation with TsCl in pyridine, which occurred exclusively at the desired site, with no side reaction with the phenol. Phenol 27 was then simply methylated under the usual conditions of MeI / K₂CO₃ / acetone, giving 28 in good yield.

The Attempted Coupling

The intramolecular coupling of 28 to give a cyclized product (scheme 11) was attempted by several methods.

First, the traditional Ullmann reaction was tried. Reaction of 28 with copper/bronze in DMF, a standard method, gave only intractable tars as products. A more current approach, as described by Riecke⁴⁹, entails the generation of active copper by reduction of CuI with Li in DME, using naphthalene as an electron carrier. Under these conditions 28 did not react at all, and the starting material was recovered.

Scheme 11

The application of the Kharasch reaction to the desired cyclization was also unsuccessful, as magnesium would not undergo insertion into either of the carbon-bromine bonds. Two methods were tried; first, simply reaction in THF with magnesium turnings, and secondly, reaction with magnesium powder and anthracene under mild sonicating conditions. The latter reactions produces "solvated" magnesium, which has been shown to produce organomagnesium compounds under mild conditions⁴⁹. Reaction of 28 with t-BuLi, to produce the corresponding organolithium derivative, gave the didehalogenated product, along with starting material, on work-up (scheme 12); seemingly, the second lithiation is much faster than the first. This may be due to the fact that t-BuLi exists as a polymeric complex; once one molecule reacts, the others in the complex are active enough that they react with the same substrate before they

Scheme 12

have a chance to leave the solvent cage. The addition of $NiCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ did not result any cyclized product. Evidently the dilithiated material does not undergo ligand exchange with the metal, or if it does, the metal does not reductively eliminate to give the desired product. The photochemical cyclisation of 28 by irradiation with UV, in a quartz container, gave an inseparable complex mixture of products.

The last approach to the cyclization used the method devised by Kumada and co-workers²². While the substrate did not react with the zerovalent nickel generated from $NiCl_2(PPh_3)_2$ in DMF, under some conditions more polar solvents may accelerate the reaction²³. Subsequent reaction, using N-methyl pyrrolidone (NMP) as the solvent, did not produce the desired material, but did yield the same dehalogenated material that was synthesized in

the reaction with tBuLi (ie. 30). Insertion of nickel into the carbon-halogen bond is occurring, but unfortunately the coupling process is not.

SUGGESTIONS FOR FUTURE RESEARCH

It is clear from this research that the intramolecular cyclization of 28, and probably systems similar to it, will be reluctant to undergo addition to transition metals and subsequent reductive elimination. This could be due to three reasons:

1. The metal adds to the tyramine moiety, but there is steric impediment to addition from the two ortho substituents on the isovanillin based moiety.
2. Addition to the tyramine moiety occurs, but further addition to the isovanillin fragment is impeded by conformational ring strain.
3. Addition to both fragments takes place, but reductive elimination is impossible due to ring strain.

Molecular modelling, specifically semi-empirical methods such as AM1 or MNDO, would normally give some insights into the reaction dynamics. Unfortunately, neither of these methods is parameterized for any transition metals. Calculations at a lower level, for example using GAUSSIAN 80, would be prohibitively expensive and time consuming.

Synthetic studies on oxazoline derivatives of isovanillic acid could lead to successful syntheses via the corresponding boronic acid derivatives using Suzuki's method⁴² (scheme 13). These derivatives are easily accessible by treatment of the ortho-lithiated oxazoline with trimethyl borate. Condensation with the tyramine fragment may even be possible using the free amine, as the condensation conditions are relatively basic in themselves.

Scheme 13

EXPERIMENTAL

General

All melting points were obtained on a Fisher-Johns hot stage apparatus are are uncorrected. Boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 683 spectrometer and frequencies are reported in cm^{-1} . Mass spectra were obtained on a VG707E instrument at the University of Ottawa. Routine proton NMR spectra were performed on a Varian EM360 spectrometer, while high resolution ^1H and ^{13}C NMR spectra were recorded on a Varian XL200 and a Bruker WM250 (at Agriculture Canada). Chemical shifts are reported in ppm (δ from TMS). Abbreviations used in the NMR description are s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad).

Thin layer chromatography (tlc) was used to monitor all reactions, and pre-coated silica gel plates (Merck 60 PF0254, 0.25 mm), were used. Plates were examined under UV irradiation followed by development with a solution of 1% ceric ammonium nitrate in 50% sulphuric acid (aq.). Preparative TLC was performed on Merck 60 F-254 plates (2.0 mm). Tetrahydrofuran (THF),

dimethoxyethane (DME), and diethyl ether were dried by refluxing over sodium in the presence of benzophenone, and collected when a deep blue colour persisted. All other solvents were distilled from reagent grade solvents unless otherwise noted.

Synthesis of 3-bromo-4-hydroxy-N-acetyl-tyramine hydrobromide (16) from 15

Phenol 15 (545 mg, 3.04 mmol) was dissolved in AcOH (10 mls) under argon. Bromine (3.10 mmol, 3.10 ml of 1M solution in AcOH) was added dropwise over 10 minutes, and the solution stirred for 2 hrs. A tan solid precipitated, and the solution became virtually colourless. The solid was filtered and washed with ether; yield 997 mg (2.94 mmol, 97%).

NMR (60 MHz): 1.80 (s, 3H, COCH₃), 2.57 (t, J = 7 Hz, 2H, β -CH₂), 3.23 (t, J = 7 Hz, 2H, α -CH₂), 6.93 (s, 2H, H-1 and H-6), 7.29 (s, 2H, H-5), 8.21 (broad s, 1H, phenolic OH)

IR (cm⁻¹): 3300 (broad, OH stretch), 1650 (amide stretch)

MS (Cl-ether): 280,278,276 (loss of NHCOCH_3), 260,258 (loss of HBr),
200,198 (loss of HBr , NHCOCH_3), 185,187 (loss of HBr ,
 $\text{CH}_2\text{NHCOCH}_3$)

Synthesis of 4-methoxy-N-acetyl-tyramine (18) from 4-hydroxy-N-acetyl-tyramine (15)

15⁴⁴ (500 mg, 2.79 mmol), K_2CO_3 (1.5 g), and MeI (1 ml) were mixed in acetone (20 ml), and refluxed for 12 hrs under argon. After cooling to room temperature, MeOH (20 mls) was added and the mixture filtered. The filtrate was passed through Celite and the solvent removed under reduced pressure, yielding 18 (405 mg, 2.10 mmol, 75%). A small sample was purified by small scale preparative TLC (30% EtOAc /Hexane).

NMR (60 Mhz, MeOD): 1.95 (s, 3H, COCH_3), 2.87 (t, 2H, $J=7$ Hz, $\beta\text{-CH}_2$), 3.42 (t, 2H, $J=7$ Hz, $\alpha\text{-CH}_2$), 3.78 (s, 3H, OCH_3), 6.86 (d, $J=8\text{Hz}$, H-3 and H-5), 7.19 (d, $J=8\text{Hz}$, H-2 and H-6)

MS: 193 (M^+), 134 (loss of NHCOCH_3), 121 (loss of $\text{CH}_2\text{NHCOCH}_3$)

Synthesis of N-acetyl-3-bromo-4-methoxy-tyramine (12) from 16

Bromophenol 16 (6.0 g, 17.7 mmol) was dissolved in acetone (50 ml) under argon. To the solution was added anhydrous K_2CO_3 (6.0 g) and MeI (12 g), and the mixture was refluxed overnight. After filtering and washing the solids with methanol (30 ml), the solvent was removed from the filtrate, the residue dissolved in ethyl acetate, and the solution passed through florisil. After complete removal of the solvent, slightly impure 12 was obtained (4.0 g, 83%). A small sample was purified by TLC (15% MeOH/ $CHCl_3$) for analysis.

NMR (60 MHz): 1.89 (s, 3H, $COCH_3$), 2.69 (t, 2H, $J = 7$ Hz, β - CH_2), 3.52 (t, 2H, $J = 7$ Hz, α - CH_2), 3.84 (s, 3H, OCH_3), 6.88 (d, 1H, $J = 8$ Hz, H-5), 7.17 (dd, 1H, $J_A = 8$ Hz, $J_X = 2$ Hz, H-6), 7.38 (d, 1H, $J = 2$ Hz, H-2), 7.85 (broad s, 1H, $NHCO$)

MS (CI-ether): 272 (M^+), 212 (loss of $NHCOCH_3$), 192 (loss of Br)

C^{13} (DMSO- D_6): 167.7 ($C=O$), 152.0 (C-4), 131.5 (C-1), 131.1 (C-2), 127.4 (C-6), 110.9 (C-5), 108.7 (C-3), 54.6 (OCH_3), 38.5 (α - CH_2), 32.0 (β - CH_2), 21.0 ($COCH_3$)

Synthesis of 2-bromo-3-hydroxy-4-methoxy-benzaldehyde (22) from isovanillin

To a solution of isovanillin (16.4 g, 0.108 mmol) in 150 mls AcOH was added, at 0° and dropwise over one half hour, Br₂ (17.3 g, 5.5 ml, 0.108 mmol); the solutions were stirred overnight. Water (150 mls) was added, and the white precipitate filtered. Recrystallization of the dried crude filter cake from EtOH (300 mls) gave 8.7 g of a pure crystalline product. After removal of 200 mls of solvent, another crop of 2.2 g was obtained, resulting in a total of 10.9 g (43%) of pure 22.

NMR (60 MHz): 3.90 (s, 3H, OCH₃), 7.00 (d, 1H, J = 9 Hz, H-6), 8.32 (d, 1H, J = 9 Hz, H-5), 10.00 (s, 1H, CHO)

IR: 1668 cm⁻¹ (C=O)

MS: 232,230 (M⁺), 231,229 (M-1), 189,187 (loss of CHOCH₂), 161,159 (loss of MeOCH₂CH=CH₂)

C13 (DMSO-D₆): 190.7 (CHO), 153.2 (C-4), 143.9 (C-3), 126.5 (C-1), 121.8 (C-6), 113.4 (C-5), 110.2 (C-2), 56.4 (OCH₃)

MP: 209 °C

Synthesis of 2-bromo-3,4-dimethoxy-benzaldehyde (23) from 22

Bromophenol 22 (5.0 g, 21.6 mmol), K_2CO_3 (3.6 g), and MeI (~7 mls) were refluxed in acetone (125 mls) under argon for 4 hrs. The mixture was allowed to cool to room temperature, filtered, and the solvent removed under reduced pressure, leaving 5.0 g (20.4 mmol, 94%) of essentially pure 23. Further recrystallization of a small sample from methanol gave an analytically pure sample.

NMR (200 MHz, DMSO D_6): 3.83 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3),

7.25 (s, 1H, H-5), 7.32 (s, 1H, H-6), 10.05 (s, 1H, CHO)

IR: 1668 cm^{-1} (C=O)

MS: 246,244 (M^+), 245,243 ($M-1$), 175,173 (loss of $MeOCH_2CH=CH$),

159,157 (loss of $MeOC=COMe$)

^{13}C (DMSO D_6): 189.89 (CHO), 154.69 (C-4), 148.85 (C-3), 126.05

(C-1), 119.03 (C-2), 116.41 (C-6), 116.20 (C-5)

MP: $148^\circ C$

**Synthesis of N-(2-bromo-3,4-dimethoxybenzyl)-4-hydroxy-phenethylamine
(25) from 23 and tyramine (24)**

Aldehyde 23 (800 mg, 3.26 mmol) and tyramine (450 mg, 3.28 mmol) were refluxed in 25 mls of dry EtOH for 3 hrs under Argon. The solution was cooled to 0°C, NaBH₄ (375 mg, 9.86 mmol) was added portionwise with stirring, and the mixture refluxed for 2 hrs. The solvent was removed under reduced pressure, 2N HCl added to the remaining solid until no further H₂ evolution was observed, and then conc. NH₄OH added until the pH was 9. The solid which precipitated was removed by extraction with ethyl acetate (30 mls), followed by removal of the solvent under reduced pressure. The crude product was passed through Florasil (in acetone), and the resulting material (1.27 g) was purified by preparative TLC (65% hexane, 25% EtOAc, 10% MeOH), leaving pure 25 (0.96 g, 2.63 mmol, 81%).

NMR (200 MHz): 2.78 (2H, broad d, J = 6 Hz, β-CH₂), 2.88 (2H, J = 6 Hz, α-CH₂), 3.69 (3H, s, OMe), 3.78 (3H, s, OMe), 3.83 (2H, s, benzyl CH₂), 6.17 (1H, s, OH), 6.68 (2H, d, J = 8 Hz, H-3 and H-5), 6.84 (1H, H-5'), 6.93 (1H, H-6'), 6.96 (2H, d, J = 8 Hz, H-2 and H-6)

MS (CI): 368,366 ($M + 1$), 288,286 (loss of C-2' to C-6' moiety of phenol ring), 260,258 (loss of 4-hydroxy toluene moiety), 231,229 (loss of phenethyl amine moiety)

^{13}C : 156.1 (C-4'), 149.4 (C-4), 148.9 (C-3'), 130.2 (C-3 and C-5), 130.1 (C-1), 129.8 (C-1'), 116.3 (C-2 and C-6), 115.9 (C-6'), 114.5 (C-2'), 114.0 (C-5'), 60.3 (OCH_3), 56.1 (OCH_3), 52.6 ($\alpha\text{-CH}_2$), 49.1 (benzyl CH_2), 34.4 ($\beta\text{-CH}_2$)

Synthesis of N-(2-bromo-3,4-dimethoxybenzyl)-3-bromo-4-hydroxy-phenethylamine (26) from 25

Phenol 25 (2.50 g, 6.83 mmol) was dissolved in 40 mls of acetic acid, with stirring. Bromine (6.9 mmol, 6.9 ml of 1M solution in AcOH) was added dropwise, and the mixture stirred for 2 hrs. The white amorphous solid which precipitated was filtered and washed with ether, yielding 26 (2.6 g, 5.84 mmol, 86%) contaminated by traces of the corresponding dibromophenol (as determined by mass spec analysis of the crude material). A small sample was purified by preparative TLC (65% hexane, 25% EtOAc, 10% MeOH) for analysis.

NMR (200 MHz): 3.03 (dt, 2H, $J_{AB} = 8\text{Hz}$, $J_{AX} = 4\text{Hz}$, $\beta\text{-CH}_2$), 3.21 (q, 2H, $J = 8\text{Hz}$, $\alpha\text{-CH}_2$), 3.82 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.26 (s, 2H, benzyl CH_2), 6.78 (d, 1H, $J = 8\text{Hz}$, H-5), 6.99 (d, 1H, $J = 8\text{Hz}$, H-6), 7.09 (d, 1H, $J = 8\text{Hz}$, H-5'), 7.12 (dd, 1H, $J_A = 8\text{Hz}$, $J_X = 2\text{Hz}$, H-6'), 7.22 (s, 1H, OH), 7.44 (d, 1H, $J = 2\text{Hz}$, H-2), 7.56 (s, 1H, NH)

MS (CI): 446,444 (M^+), 366 (loss of bromine), 260,258 (loss of 4-ethyl phenol from 366), 231,229 (loss of 4-hydroxy-phenethyl amine from 366)

C^{13} : 152.7 (C-4), 149.8 (C-3), 148.1 (C-4'), 132.7 (C-2), 129.5 (C-6), 129.0 (C-1'), 128.9 (C-6), 122.7 (C-1), 116.3 (C-5), 115.2 (C-6'), 114.9 (C-5'), 114.5 (C-2'), 109.1 (C-3), 55.9 (OMe), 49.2 ($\alpha\text{-CH}_2$), 47.5 (benzyl CH_2), 30.0 ($\beta\text{-CH}_2$)

Synthesis of N-tosyl-N-(2-bromo-3,4-dimethoxybenzyl)-3-bromo-4-hydroxy-phenethylamine (27) from 26

Amine 26 (445 mg, 1.0 mmol), pyridine (1 ml), and TsCl (200 mg, 1.05 mmol) were stirred in 5 mls of DME under argon for 36 hrs. Ethyl acetate and

water (20 mls of each) were added, followed by 10 mls. of 3M HCl and then saturated aqueous NaHCO_3 . The organic phase was dried with sodium sulphate and removed under reduced pressure, leaving 560 mg (0.91 mmol, 91%) of 27. A small sample was purified by TLC (65% hexane, 25% EtOAc, 10% MeOH) for analysis.

NMR (250 MHz): 2.43 (s, 3H, tosyl CH_3), 2.57 (t, 2H, $J=8\text{Hz}$, $\beta\text{-CH}_2$), 3.32 (t, 2H, $J=8\text{Hz}$, $\alpha\text{-CH}_2$), 3.78 (s, 3H, OMe), 3.89 (s, 3H, OMe), 4.42 (s, 2H, benzyl CH_2), 6.82 (d, 1H, $J=8\text{Hz}$, H-5), 6.88 (dd, 1H, $J_A=8\text{Hz}$, $J_X=2\text{Hz}$, H-6), 7.03 (d, 1H, $J=9\text{Hz}$, H-5'), 7.10 (d, 1H, $J=2\text{Hz}$, H-2), 7.21 (d, 1H, $J=9\text{Hz}$, H-6'), 7.42 (d, 2H, $J=8\text{Hz}$, H's ortho to tosyl methyl), 7.77 (d, 2H, $J=8\text{Hz}$, H's ortho to sulphonamide)

IR: 3600-3100 (OH)

MS (CI): 602, 600, 598 (M^+), 522, 520 (loss of Br), 414, 412 (loss of 3-bromo-4-hydroxy-toluene), 382, 384 (loss of 1-bromo-2,3-dimethoxy-benzene), 229, 231 (2-bromo-3,4-dimethoxy benzyl cation), 149 (N-methyl-tyramine iminium ion)

^{13}C (250 MHz): 154.3 (C-4), 153.6 (C-3'), 151.7 (tosyl C-4), 144.5 (C-4'), 138.2 (C-1), 134.0 (C-2), 132.5 (C-1'), 130.8 (tosyl C-2 and C-6), 130.0 (C-6), 129.6 (tosyl C-1), 128.3 (tosyl C-3 and C-5), 126.6 (C-6'), 117.4 (C-5), 112.8 (C-5'), 110.3 (C-3), 60.5 (OMe), 56.6 (OMe), 52.7 (benzyl CH_2), 51.2 ($\alpha\text{-CH}_2$), 34.7 ($\beta\text{-CH}_2$), 21.4 (tosyl CH_3)

Synthesis of N-(2-bromo-3,4-dimethoxybenzyl)-N-tosyl-3-bromo-4-methoxy-phenethylamine (28) from 27

Phenol 27 (650 mg, 1.08 mmol), K_2CO_3 (500 mg), and MeI (2 ml) were refluxed in 20 mls of acetone for 6 hrs under argon. After allowing to cool to room temperature, excess water and ether were added, and the organic phase washed with 2N HCl (10 mls). After removal of the solvent, essentially pure 28 (375 mg, 0.612 mmol, 57%) remained. A small sample was purified by TLC (ether) for analysis.

NMR (250 MHz): 7.75 (d, 2H, $J=8\text{Hz}$, tosyl H-2 and H-6), 7.33 (d, 2H, $J=8\text{Hz}$, tosyl H-3 and H-5), 7.22 (d, 2H, $J=9\text{Hz}$, H-6'), 7.10 (d, 1H, $J=2\text{Hz}$, H-2), 6.95 (dd, 1H, $J_A=8\text{Hz}$, $J_B=2\text{Hz}$, H-6), 6.87 (d, 1H, $J=9\text{Hz}$, H-5'), 6.75 (d, 1H, $J=8\text{Hz}$, H-5), 4.45 (d, 1H,

$J_{\text{gem}} = 7\text{Hz}$, benzyl CH_2), 4.43 (d, 1H, $J_{\text{gem}} = 7\text{Hz}$, benzyl CH_2), 3.89 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.34 (t, 2H, $J = 8\text{Hz}$, $\alpha\text{-CH}_2$), 2.62 (t, 2H, $J = 8\text{Hz}$, $\beta\text{-CH}_2$), 2.44 (s, 3H, tosyl CH_3)

MS (CI): 616, 614, 612 (M^+), 536, 534 (loss of Br), 414, 412 (loss of 3-bromo-4-methoxy-toluene), 398, 396 (loss of 1-bromo-2,3-dimethoxy benzene), 380, 378 (loss of Br, tolyl sulphone), 229, 231 (2-bromo-3,4-dimethoxybenzyl cation), 149 (N-methyl-tyramine iminium ion)

^{13}C (250 MHz): 154.4 (C-4), 152.9 (C-3'), 146.1 (tosyl C-4), 143.3 (C-4'), 136.5 (C-1), 133.2 (C-2), 131.8 (C-1'), 129.6 (tosyl C-2 and C-6), 129.5 (tosyl C-1), 128.5 (C-6), 127.0 (tosyl C-2 and C-5), 125.5 (C-6'), 118.9 (C-3), 113.7 (C-5), 111.8 (C-5'), 111.3 (C-2'), 60.1 (OMe), 55.9 (OMe), 55.8 (OMe), 51.6 (benzyl CH_2), 50.0 ($\alpha\text{-CH}_2$), 33.7 ($\beta\text{-CH}_2$), 21.1 (tosyl CH_3)

Attempted synthesis of 1,2,12-trimethoxy-5,6,7,8-tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28

Dibromo compound 28 (42 mg, 0.0685 mmol), $\text{NiCl}_2(\text{PPh}_3)_2$ (45 mg, 0.0688 mmol), and lithium iodide (37 mg, 0.274 mmol) were stirred in 2 mls of degassed, dry DMF under argon. The mixture was heated at 60° for 12 hours. The starting material was unchanged.

Attempted synthesis of 1,2,12-trimethoxy-5,6,7,8-tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28

Dibromo compound 28 (20 mg, 0.0326 mmol) and copper/bronze (200 mg) were refluxed in 1 ml of dry, degassed DMF for 1 hour under argon. Intractable baseline materials were obtained.

Attempted synthesis of 1,2,12-trimethoxy-5,6,7,8-tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28

Activated copper was prepared according to Riecke⁴⁹. A mixture of CuI (485 mg, 2.55 mmol), K (100 mg, 2.56 mmol), and naphthalene was stirred under argon in 3 mls of dry DME for 8 hrs. Dibromo compound 28 (45 mg,

0.0734 mmol) in 2 ml dry THF was added and the mixture refluxed for 4 hrs. TLC showed no indication of reaction.

Attempted synthesis of 1,2,12-trimethoxy-5,6,7,8-tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28

According to a method by Suzuki et al⁴², 28 (18.0 mg, 0.0293 mmol), Pd(PPh₃)₄ (1.0 mg, 0.86 mol, 3 mol%), Na₂CO₃ (1 ml, 2M aqueous sol'n), and toluene (2 ml) were refluxed for 24 hrs under Ar. No reaction had occurred. The same reaction, in the presence of H₂NNH₂ (1 ml) and Bu₄N⁺Br⁻ (5 mg) also failed to produce any product.

Attempted synthesis of 1,2,12-trimethoxy-5,6,7,8-tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28

According to a method by Bonnemann et al⁵⁰, dibromo compound 28 (18 mg, 0.0293 mmol) and Mg powder (excess) were stirred in dry THF (2 ml) under Ar. The reaction vessel was placed in an ultrasound cleaning apparatus, and the stirring continued for 12 hrs. No reaction was observed by TLC.

Attempted synthesis of 1,2,12-trimethoxy-5,6,7,8-tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28

28 (18 mg, 0.0293 mmol) was dissolved in dry DME (2 mls) in a quartz round bottom flask, and irradiated in a UV chamber. The reaction was monitored by TLC every 1/2 hour. Over the course of 3 hrs, the starting material disappeared, leaving only baseline material and traces of a few poorly resolved materials.

Attempted synthesis of 1,2,12-trimethoxy-5,6,7,8-tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28

28 (18.0 mg, 0.0293 mmol) was dissolved in dry THF (2 ml) and cooled to 0°C under Ar. T-BuLi (0.05 ml, 1.25 M, 0.0625 mmol) was added; TLC indicated the consumption of the starting material and the appearance of a new material (30). Pd(PPh₃)₄ (10 mg) was added, and the mixture removed from the ice bath. No further products were observed by TLC. The same procedure, using NiCl₂(PPh₃)₂ instead of the palladium catalyst, also resulted in no new materials. The pale yellow amorphous solid 30 was purified by preparative TLC (ether), resulting in 11 mg of pure material.

The experiment was repeated using only 1.0 equivalents of tBuLi, and no organometallic catalyst. Unchanged starting material (9.9 mg, 0.0161 mmol, 55%) was recovered, along with the dibrominated material 30 (5.0 mg, 0.0111 mmol, 38%).

NMR (250 MHz): 2.43 (s, 3H, tosyl methyl), 2.58 (t, 2H, $J=8$ Hz, β -CH₂), 3.24 (t, 3H, $J=8$ Hz, α -CH₂), 3.75 (s, 3H, OMe), 3.79 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.25 (s, 2H, benzyl CH₂), 6.76 (s, 1H, H-2'), 6.87 (d, 2H, $J=8$ Hz, H-3 and H-5), 6.72-6.81 (m, 4H), 7.31 (d, 2H, $J=8$ Hz, tosyl H-3 and H-5), 7.73 (d, 2H, $J=8$ Hz, tosyl H-2 and H-6)

MS (CI): 456 ($M^+ + 1$), 455 (M^+), 318, 151 (base peak), 149

¹³C: 158.3 (C-4), 149.4 (C-3'), 148.9 (tosyl C-4), 143.3 (C-4'), 137.4 (C-1), 130.7 (tosyl C-1), 129.8 (C-2 and C-6), 129.7 (tosyl C-2 and C-6), 128.8 (C-1'), 127.3 (tosyl C-3 and C-5), 120.9 (C-6'), 113.9 (C-3 and C-5), 111.5 (C-2'), 111.0 (C-5'), 55.9 (OMe), 55.8 (OMe), 55.1 (OMe), 51.9 (benzyl CH₂), 49.3 (α -CH₂), 34.3 (β -CH₂), 21.3 (tosyl CH₃)

Attempted synthesis of 1,2,12-trimethoxy-5,6,7,8- tetrahydro-6-tosyl-9,13-metheno-13H-benz-6-azacycloundecine (29) from 28

Dibromo compound 28 (20 mg, 0.0326 mmol), $\text{NiCl}_2(\text{PPh}_3)_2$ (1.0 mg, 0.00153 mmol), KI (5 mg, 0.030 mmol), triphenyl phosphine (3 mg, 0.011 mmol), and zinc powder (3 mg, 0.046 mmol) were stirred in dry DMF (1 ml) under argon overnight, and then refluxed for three hours. TLC showed that the starting material was unchanged.

Substitution of N-methyl pyrrolidone for DMF in the above reaction resulted in the isolation of 30 (~80%), after work-up with water / CH_2Cl_2 and preparative TLC (40% EtOAc/Hexane) purification.

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