

# Entering Modeling Space

## An Apprenticeship in Molecular Modeling

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**Abstract:** Twenty years ago computer modeling had made its first major impact on the chemist's patterns of thought. Now it is prominent in research and graduate education, and has made its presence felt throughout the undergraduate curriculum. I describe two consultations with chemists specializing in synthesis, by which I intend to illustrate (1) attitudes of novices to the craft; (2) experiences in apprenticeship which include flights of depression, disillusion, and elation; and (3) changes in their judgment of computer modeling as they make it part of their armory of concepts and images. The examples treat aspects of the chemical system not easily incorporated into structural formulas (chirality) and even physical models (relative energetics), but which are offered in computer modeling systems with molecular mechanics or quantum mechanical energy estimators. On the way, we can arrive at a notion of the changing value of computer modeling, and its impact on the chemist's frame of mind.

**Keywords:** *molecular modeling, molecular mechanics, electronic structure, computer graphics, chemical education.*

## Introduction: Chemical Speculation, a Glass Bead Game

In graduate school one learns to handle materials safely, follow experimental protocols, operate various types of equipment, interpret analytical profiles (*i.e.*, pictograms which may be spectra, radiographs, or generally response curves from instruments' processing of electrical or optical signals), and keep careful records. To master the various skills and habits of thought implied by these operations is no small achievement. However, at our university and others, the apprentice is not fully welcomed into the community of scholars unless and until she gives evidence of creative thought. The medium in which the creation is expressed is not *matter* – the apprentice does not construct a

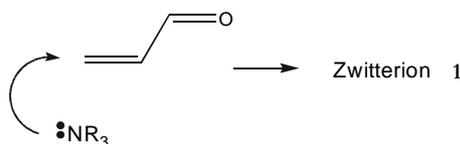
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masterwork in material to be purified, analyzed and characterized. Rather the creation is an arrangement of symbols, a kind of glass bead game. Reference to the stuff of chemistry is indirect. Rather more immediately, the work alludes to the chemical literature, itself encoded symbolically, and is strengthened by the subtlety and intricacy of its interweaving with existing reports. The work to be judged is called a research *proposal*, and the fiction is maintained that in some potential world there would result a series of manipulations, purifications, and transformations in materials corresponding closely to the narration. In this memoir, we relate two views of apprenticeship, in which computer modeling is incorporated in the first case into a proposal, and in the second into an explanation of data. The very theoretical medium of computer modeling enters naturally into the very theoretical language of the research proposal and the mechanistic speculation, and can somehow augment and reinforce the hopeful conjecture. But from what source does the authority of the computer model derive? If it did seem necessary to resolve ambiguities left open by the normal symbolic language of structural formulas, how is it that computer modeling was seen as adequate to the task? (We do follow success stories.) What made the results of computer modeling convincing?

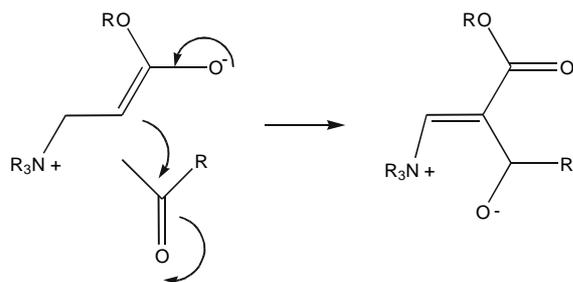
## I. A Research Proposal

### 1. The Use of Symbols of Structural Formulas

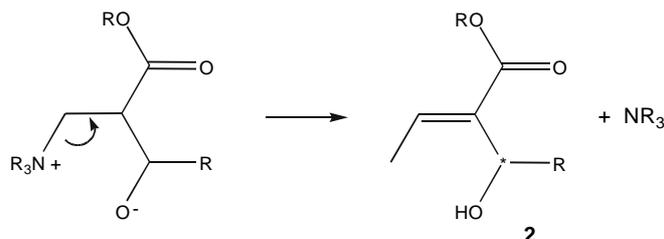
We treat first a research proposal constructed by a graduate student (van Divender 1999). We need to employ some of the symbolic language of chemistry (Hoffmann 1995, sects. 14-15) to express the original notion at the heart of the proposal.



The base  $\text{NR}_3$  participates as a catalyst in preparing **1**, the reactive ‘zwitterion’, shown in the next structural diagram, which then attaches itself to an aldehyde.



The system expels the  $R_3N$  base, producing the product **2** shown below.



The reaction represented by this series is named the Baylis-Hillman reaction and well understood experimentally (Bode & Kaye 1991). A notable feature of this reaction is that a new asymmetric center appears, marked by the asterisk. This will be the focus of the apprentice's research proposal.

We might pause to reinforce our observation that the work of the apprentice has begun with the structural formula shorthand, a symbolic representation of the fundamental units of the chemist's mental model of the molecule, *i.e.* atoms, bonds, and electron pairs. As many have noted, this medium is ideally suited to emphasize key features of a chemical process while capable of suppressing any distraction. Rearrangements of these symbolic or linguistic elements in a kind of abstract space (through which chemists communicate) are representations of potential chemical transformations in real space. It is the plausibility and significance of proposed transformations that are at issue here, and these qualities of the representation are the basis for judgment of the competence of the apprentice. However, the ultimate test of those qualities, transformation of substances in the laboratory, is not to be conducted. There are excellent reasons: the ultimate test is likely to be expensive, time demanding, and uncertain of success. Success may be the ultimate test of the validity of the novice's suggestion, but it is the ability of the apprentice to manipulate the language of chemistry that is to be judged. One may well (and often) consider the novice's speculation to be evidence of a subtle and powerful scientific mind, and still be skeptical of the ultimate outcome of the work proposed.

The symbolic representation of the Baylis-Hillman reaction has so far been entirely adequate to the task of description. Literature reports of the slowness of the reaction, and the difficulty in generating products of specifically desired chirality constitute a problem worthy of consideration: how can the reaction be accelerated, and how can the product chirality be controlled? These aspects of the molecule – one geometrical, one energetic – are not naturally incorporated into the molecular sketch.

## 2. Representing Chirality

The notion of chirality deserves discussion, since the molecular sketch must be subtly elaborated to represent this structural feature. Other models must be employed to guide the construction and interpretation of the sketch.

We celebrate (Rouhi 1999) the insight of van't Hoff (and in rough parallel, Le Bel) who are distinguished in the history of chemistry for taking the leap into the three-dimensional representation of molecules with physical models. The tetrahedra of van't Hoff were so simple and elegant a representation and explanation of the phenomena of optical activity and isomer counts, that though there were scoffers offended by the audacity of the young man, his models were generally accepted immediately. The third dimension (3D) was a key, since mirror images of planar objects must be equivalent. The third dimension is of course not absent from the usual first discussions of chirality and chiral recognition – the hand in glove and the foot in shoe are analogies depending for their power on tactile experience in the 3D macroscopic world. The sketch however, confined to two dimensions and borrowing only crudely from the code of perspective drawings, is not so effective in conveying the sense and nature of chirality (Hoffmann 1995, sect. 9). It can incorporate reminders of the 3D character of the tetrahedron – depth clues – but the success of such reminders must depend on the experience in 3D of the user of the sketch.

## 3. Inducing Chirality

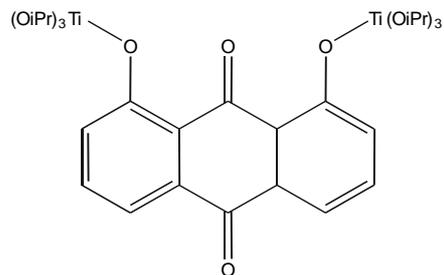
Since the product **2** above is chiral, one may hope to produce an excess of one optical isomer by clever management of reaction conditions. The departure in the reaction from enantiomeric equivalence – in which the two possible optical isomers appear in equal amounts – can in principle derive from asymmetry anywhere in the reaction milieu. The aldehyde, the base, and the acrylate **1** have been made chiral, with varying degrees of success in producing an excess of one or another optical isomer of the adduct. The original suggestion in the proposal was to complex the acrylate with a chiral Lewis acid, which might both activate the system and speed the reaction, and by its chirality favor one adduct isomer. The presence of an acid required that the amine (base) co-

catalyst not be employed; a phosphine (that would not react with the acid) would take its place.

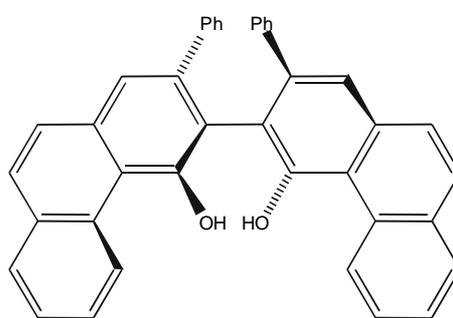
The Lewis acid is to be formed from an achiral titanium species and a chiral 'vaulted 3,3'-biphenanthrol', which has a two-fold axis of symmetry (not a mirror plane). Here the two-dimensional representation becomes so unwieldy that it begins to lose its utility as a model.

Departures from coplanarity of the two phenanthrene rings are suggested by the bold and broken lines in the diagram of S-VAPOL; atoms at the thick end of the bold wedge are close to the viewer (in front of the plane of representation). Atoms at the end of a broken line are remote from the viewer (behind that plane).

It is left as an impossible exercise, to construct a sketch of the molecule resulting from the attachment of the S-VAPOL to a Titanium atom in the Lewis acid through two oxygen atoms, after splitting out two water molecules.



Lewis Acid



S-VAPOL

#### 4. Beyond the Icon

It was here that familiar physical models failed as well. Their sheer bulk, their tendency simply to fall apart of their own weight, and their ability to assume all torsional arrangements in which atoms and bonds (*i.e.*, their physical representations, balls and sticks) were not actually in collision left them inconvenient to handle and ambiguous in their implications.

When a model fails, the next step is often to elaborate the model. Rather than a typical ball-and-stick physical model, one could have constructed a space-filling model. While more 'realistic' in some ways, these objects are generally not as informative as ball-and-stick models, are more difficult to manipulate, and rule out only the conformations in which the spheres assigned to atoms collide. It was at this stage that computer graphics and com-

puter-based (enabled) energy modeling presented itself as an attractive technique.

The appealing feature of computer graphics and associated energy-estimating systems (molecular mechanics, to begin with) is that they promise exactly the information lacking in the abstract<sup>1</sup> model (the sketch) and the iconic model (the physical object). That is an estimate of the relative energy of atomic arrangements, built into an abstract mathematical representation which is expressed on a computer display that has some of the qualities and appeal of the iconic model.<sup>2</sup> But are we to believe such promises? On what foundation do they rest? Moreover, can the computer-contained analogic system be considered a desirable model? We will return to these questions, as our story matures.

## 5. First task: Translating the Sketch

The first task of the modeler of a molecule of any complexity is to produce some reasonable first guess of the connections among atoms, and their arrangement in 'space'. The space of the computer's drawing field is familiarly two-dimensional (Trindle 1989); so many computer modeling systems accept a sketch and project it into an abstract three-dimensional space. That set of Cartesian (or equivalent) coordinates in 3D space then defines a set of projections onto the 2D display. It is also frequently the case that a preliminary refinement of the structure is performed, so that conventional bond lengths at least, and usually familiar bond angles are imposed.

This surely seems innocuous, a mere convenience which is more or less equivalent to what the reader of a molecular sketch does. However, it is the first of several significant steps in which a task of interpretation is given over to an inhuman agent that does not carry the wishes and insights of the chemist. Often, early in practice with the drawing system, the intended arrangement of atoms defined in the sketch and its computer-equivalent display, is transformed out of recognition by criteria of the program of what constitutes a stable molecular structure. Giving over the task of interpretation is a surrender of control. The question is of course: what compensation is given?

## 6. Imposing our Will?

Our apprentice was frustrated by the quirks of our particular drawing system (Hyperchem™ 1996) – the details need not detain us – but was more seriously taken aback by the measures we could take to overcome the built-in preferences of the system. To take a small example, there are several neighbors of each titanium in the anthroquinone Lewis acid: three *isopropoxides* (called OiPr in the sketch, more carefully written as  $-\text{O}-\text{CH}(\text{CH}_3)_2$ ) and an oxygen from the large ring system. Four-coordination, by the rules built into our

software, means a tetrahedral geometry. But what of the nearby oxygen doubly bound to the central ring of the anthroquinone? It can be coordinated simultaneously with each titanium. We must choose whether to draw a bond from Ti to the central O and make a fifth neighbor. There must also be a coordination site available for an approaching ligand, if the system is to function as a Lewis acid and bind an electron pair from the reacting methyl acrylate. The coordination seems to vary from four (or five?) to six, depending on the stage of the reaction. The modeling system would present discontinuous geometry changes, from tetrahedral to trigonal-bipyramidal to octahedral in the process, which does violence to our preconceptions of a relatively stable structure for the catalyst. A related puzzle was thrust upon us as we brought together the anthroquinone and the titanium isopropoxides. Our preconception, based perhaps on no more than an expectation of octahedral coordination at the critical stage of the reaction but not contradicted by our iconic models, was that the anthroquinone would define a plane in which we would find both titanium atoms and two of their other ligands. Instead, the reported stable structure folded the anthroquinone out of such a plane. Simply to preserve our preconceptions, nourished from half-remembered X-ray structures at best, and perhaps a wish for symmetry and beauty, we used the power conceded to us by the program's designers to impose constraints on the molecule in question. We *forced* the coplanarity that the system would not grant within its set of laws and rules of thumb.

The result was pleasing in appearance. However, the question hung in the air: if we can impose our own requirements on the model, can we rely on the reports of the computer system? Has it not lost whatever virtue its objectivity, its enforced separation from our hopes and dreams, can bring?

Of course, if the modeling system (however bullied into submission) would still not illustrate the proposal, this question would not need serious response. We can set aside the question for the time.

## 7. Questions Answerable and Not

The next task was to introduce the chiral S-VAPOL species as a ligand. A series of questions needed attention. In the two pseudo-octahedral coordination sites for each of the titanium atoms, four are potentially available to new ligands. There are two polar sites and two equatorial sites; bidentate S-VAPOL requires two. Would the Lewis acid accept two S-VAPOL ligands, or would it prefer only one? For the first added S-VAPOL, would a single titanium atom provide both attachment sites or would each titanium atom provide one (the 'bridging' case)? If the former, would the two sites each be equatorial, or would an equatorial-axial (polar) pair of attachment sites be preferred? Would the result differ if the optical isomer R-VAPOL were cho-

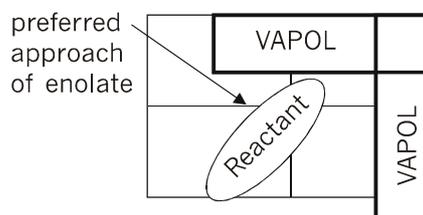
sen rather than S-VAPOL? These are precisely the kinds of questions which energy modeling (molecular mechanics) was designed to address. However, would this particular modeling system, which includes only the most primitive force fields for metals, produce trustworthy results?

Molecular mechanics, an analogic model for all its mathematical abstraction, requires a considerable dosage of experimental fact. The quantities ('parameters' of the model) by which the analogy is realized are evaluated as to match structures and sometimes energies for well-understood systems. The modeling system is 'calibrated' in this way, and one has confidence precisely to the extent that the system under investigation resembles the calibration set. In our case, the analogy is not well tested, the system under investigation is so different from the members of the calibration set, that one should have no exaggerated expectation of its success (or if successful, the significance of its good fortune.) We are in unfamiliar territory, with a guide of little plausibility. But like explorers before us, we press on.

Our hope was realized. That is to say, the S-VAPOL binds to a single titanium, at equatorial and axial positions (a-e binding). With the help of the computer display, we were able to distinguish two kinds of a-e binding, and to believe the system's report that one was much more stable. The bridging alternative is much less favored by our modeling system, and a second S-VAPOL is hard to introduce into the Lewis acid.

With a plausible structure for a chiral catalyst, the next step is to characterize the binding of the substrate aldehyde. This is the species to which a new carbon center is to be defined, with, so one is hoping, controlled chirality. The only chirality in the modeled system thus far is in the Lewis acid catalyst, but its influence on the potentially chiral ('prochiral') substrate is critical to the success of the proposal.

A great simplification of the catalyst topography can be helpful here. The rectangular figure shows a caricature<sup>3</sup> which takes us back from the complexity of the analogic model to a more immediately visualized representation. The rectangle that encloses our entire molecule is bisected twice, by a horizontal line and a vertical line. Our line of sight toward the Lewis acid passes through their intersection. The titanium atoms lie to the left and right of the intersection along the horizontal line, which defines the plane of the anthroquinone. The line of sight is the way the C=O bond of a reactant aldehyde might coordinate with the vacant Titanium coordination sites of the Lewis acid.



Once again we intervened in the process of modeling, since the system itself refused to coordinate the C=O oxygen along the axis so simple to define in a sketch. We aligned it by imposing constraints, *i.e.* our will. The question already posed (*if we can impose our own requirements on the model, can we rely on the reports of the computer system?*) troubled us somewhat less than it had, for reasons easy to understand (we were hot on the chase) but not so easy to defend.

## 8. Modeling and Mood Swings

The last remark might suggest that we were becoming hardened to the need to intervene in the operation of our modeling system. We should disclose here that *modeling causes mood swings*. We were so elated when the system would push our molecule into a plausible form, and were so devastated when there would not appear in the modeling aspects of the system what we *knew must be*, that we can hardly claim to be the dispassionate investigators so familiar in the simplest accounts of scientific work. In this case of course the success of the modeling was critical to the rite of passage of the apprentice, already described. But more than that, the system was a third party endorsing or denying our mental models, our chemical intuition, our grasp of our field. We felt great guilt in imposing our preconception; we knew we were tampering, but was this intervention an improvement and refinement of the model or simply cheating? Could we get *any result we wanted* by sufficient fiddling? This problem crops up in many theoretical investigations. In the most subtle and abstract modeling of electronic structure, it is possible to execute a series of calculations of varying levels of sophistication and find conflicting results. What does one conclude, if the least accurate calculation 'explains' or 'reproduces' experimental data, but more difficult, subtle, and confidence-inspiring calculations fail to do this fundamental task? One can hardly say that a consistent policy is abroad in the land. Practice is divided; there are those who have an exaggerated respect for experimental data (typically, theoreticians), and those who have an exaggerated respect for calculations (mostly experimentalists, though this rule is weaker).

## 9. Modeling Bond Making Without Electrons

Molecular mechanics includes a bond, or leaves it out. There is no natural incorporation of bonds forming or changing type. Thus, the modeling system is in principle incapable of adequate description of the Baylis-Hillman reaction's transition state, in which several bonds are in that awkward in-between stage, becoming or disappearing. Still the question before us finally requires a judgment on the nature of a reaction path. We evaded the paradox in the following way.

We needed to judge the hospitality of the aldehyde (as bound to the chiral catalyst) to an approaching enolate. To do this we ‘tethered’ an enolate 5 Å away from the carbon center to which it would be eventually attached. Depending on our starting point, we found that under this constraint the enolate migrated into the upper left quadrant. The separation of 5 Å was sufficient that no bond would be formed even in a realistic model capable of description of such an event. The energy field, defined by the van der Waals and electrostatic charges well incorporated into the molecular mechanics description would act as a long-range guide to the enolate’s approach. We argued that this would determine the course of the reaction long before arrival at the critical site of the transition state.

In this way, we established to our satisfaction that S-VAPOL ligand blocks approach from the upper right quadrant of the figure. It seemed that the ligand’s bulk also forces the bulky substituent of the attached aldehyde away from that quadrant. This exposes one face of the aldehyde to the final reagent, a phosphine-activated enolate (methacrylate in the model).

Here is the way the results of this shady practice appeared in the research proposal.

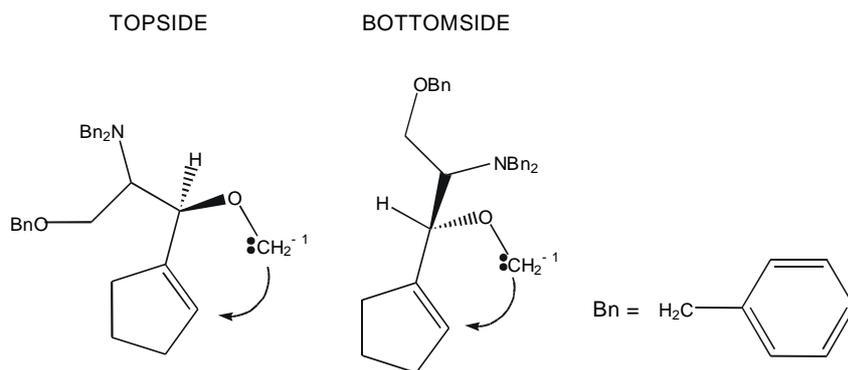
As shown [...] when (*S*)-VAPOL binds [to the Lewis acid] nucleophilic attack occurs on the *si* face of the aldehyde. Likewise, (*R*)-VAPOL shields the *si* face of the aldehyde to provide the corresponding enantiomer. [The model] illustrates the energetic preference of the aldehyde (pivaldehyde here) to cant away from the bulky chiral ligand, setting up an asymmetric environment [that] allows this reaction to occur preferentially at one face of the aldehyde. With the VAPOL ligand occupying what might be considered the upper and lower right quadrants [...] and the aldehyde canting downward into the lower left quadrant, the only approach remaining to the enolate is that from the upper left as shown.

Behold the sturdy buttresses of the repeated phrase “as shown”, which plainly pleads the obvious truth of the enclosure. And who could doubt such confident assertions as are to be found therein? In the event, the results of the modeling were helpful to an otherwise thorough and clearly presented research plan. The exercise did in fact add value to the work of the apprentice.

## II. Explanation of data

### 1. The Mechanistic Conjecture

It is not only the apprentice who enters modeling space unsure but hopeful of the welcome that foreign land will give. Experienced chemists, turning their hands to the elusive reaction path and its landmark transition state, will welcome any means of understanding that which experiment cannot illuminate. Small effects beyond any reasonable hope of modeling still need explanation. The question (in part) bears on the relative energy of transition states first drawn by the investigators as shown in the example below:



There is evidence for reversal of the favored path, from backside attack in polar medium, to topside attack in nonpolar medium. In the terse expression of the technical report:

This distinct selectivity difference led us to examine possible transition states in an effort to rationalize these results [Hart & Etzkorn 1999].

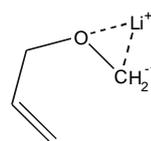
But how to do this examination of an experimentally inaccessible structure, is the question. Here computer-assisted modeling's promise is particularly seductive. Even to begin requires a conscious compromise, however. The capacity of our computer system being limited, the 'Bn' = C<sub>7</sub>H<sub>7</sub>-species, which is so prominent in the experimental system, puts the molecule beyond our reach, particularly if we want to bring to bear the more powerful but computationally demanding techniques of electronic structure modeling. This would be required to make plausible speculations on differences between transition states. We replaced Bn and OBn fragments with CH<sub>3</sub> (methyl) to make the problem manageable. Of course, we could not be fully confident that by this modeling step we were capturing the critical aspect of the experimental system's behavior. This winnowing and paring, forced by necessity, is common practice and the essential task of modeling. Furthermore, chemists

are happy to believe that reactions are local phenomena; but that does not make our pruning trustworthy. The first idea of the experimental investigators was that the critical distinction between transition states would be steric, *i.e.*, referring to the spatial demands of the several structures. In our simplification we might have ruled out of court the best explanation of the chemical behavior.

## 2. Modeling Bond Making With Electrons

The fundamental chemical process, bond making, requires for its description the most abstract of models, quantum mechanics, and its translation into the structural language (the universal model) of practicing chemists. The achievement of a practically fast and accurate electronic structure modeling system is an achievement of the past twenty years that is recognized by the Swedish Academy as a step of highest significance. No chemist is far away from a highly capable system of this kind, which can be realized by an inexpensive personal computer. If, on occasion, the makers of the theory software and displays have worried about that they were placing their technology in the hands of people too ill-prepared to use it wisely, they had many precedents, back to Prometheus.

We had available results of a prior electronic structure modeling of the Still-Wittig transition state for a much smaller system, allyl lithomethyl ether (Wu & Houk 1990). We were easily able to reproduce the published structure of this small system, a tribute to advances in computer capability and of course to those who showed the way. We quickly came to agreement with that report that the Lithium counter-ion (though not shown in the first sketch above) was intimately involved in the Still-Wittig transition state.



Allyl lithomethyl ether

That is, try as we might to construct a transition state of the type the investigators had drawn, we were unable to enforce our wishes. We could constrain the anion to a form where the new bond from the carbanion site ( $\text{CH}_2^-$ ) to the unsaturated  $\text{C}=\text{C}$  terminus was not completely established but was beginning to close. However, once we relaxed constraints, the system collapsed to complete the bond. With lithium present, we could locate transition states with ease. This behavior strengthened our confidence in the model, simply because it was not infinitely malleable; it had principles it would not abandon. Even better, the computational system, left to its own devices, did report that the transition states in which the Li cation is bound to N and O favored a topside arrangements while in the transition states where the Li cation is coordinated to the ether oxygen and a solvent oxygen, the bottomside approach is favored. Simply because we took no measures to

impose our wishes on the system, apart from offering for judgment some structures we had drawn, the system fulfilled its role as impartial evaluator.

### III. Conclusion

#### 1. Is a Computer-Bound Modeling System a Valuable Model?

Perhaps with the context of these adventures, we are able to come to a judgment whether the molecular modeling system described meets criteria for a useful model. According to a previous discussion (Trindle 1984), a model should be memorable, simple, self-consistent, powerful, and flexible. Any model that meets these criteria would surely be persuasive as well. However, we might suspect that a model can be persuasive not for these excellent reasons, but for ones less admirable and respectable.

Unfortunately for the repute of the molecular modeling related in our story, one can hardly say that the system is *memorable*, *i.e.*, easy to hold in mind. In fact, to the extent that the manipulations in the computer code are withheld from the user, the system declines to be held in mind. (Perhaps the results especially the graphic presentations as shown are striking, but that is another story, about a version of the iconic modeling borrowed for the purpose of display.) The elaborate calibration and parametrization (the preoccupation only of specialists), inescapable parts of modeling systems, must mean that the system is not *simple* in any fundamental way. Perhaps the user interface makes the choices seem simple, but that too is another story. Whether the model is *self-consistent* is hard for the user to appreciate. That property can be revealed by paradoxes in reports, but only in the same unfortunate way that the collapse of a bridge reveals error in design.

The user can come to a more reliable judgment on how *powerful* the modeling system might be, but even here pitfalls abound. One may require that the modeling system be faithful to known results (even those which were counter-intuitive and for which other representations failed), and report aspects of chemical systems which are independently verifiable. This is of course scientific investigation compactly defined, and may be the justification for the modeling in our story.

The design of the software system defines its *flexibility*; some systems permit the user to augment or alter the parameter set, so to treat unusual atoms, bond types, *etc.* Others block all modification, for good or ill. Our system permits such modification, and also accommodates atoms by an interesting process of defaults. Every atom is assigned a radius, and the number of

linked neighbors will define ideal bond angles for atoms not otherwise defined in local geometry.<sup>4</sup> The system also draws analogies, and estimates a missing parameter defining the stiffness of a valence angle bend X-Y-Z by searching its data base for X-Y-\* (\* arbitrary). This process is risky, and is properly disclosed in documentation and in a brief message to the user to the effect that 'a default bending parameter' was used. As we saw, defining constraints extends the range of chemical species and behavior treatable in the system. However, the recommended attitude toward these estimates is distrust, and the message should be treated as a warning to be taken seriously.

One might judge the value of a model by its contribution to the everyday thought of a practitioner. Every chemist is fluent in the abstract language of structural formulas; some convey only pedestrian thoughts, while others express their genius. A paper napkin can hold a stroke of insight in a sketch, if not so simple and pregnant with implication as  $F=ma$  or  $E=mc^2$ . But the napkin, and the symbols thereon, are primarily an expression of the chemist's judgment and not much of a corrective. While not as common as pencil and paper, computer assisted modeling is accessible to most chemists. As this trend becomes more pronounced, perhaps we will be able to say that the balance will shift, and that a part of the judgment of the expert chemist will come to reside in the machinery rather than the person. With due respect to the knotty issues raised in Searle's Chinese-translating system, we might be unsurprised at this continuation of a trend begun with the stereomodels of van't Hoff and le Bel.

Computer models do not seem to fare so well in the criteria for an ideally valuable system, but its persuasive power is considerable. Our apprentice was able to produce a picture – a summary of all the labor of the exercise – and present it as (first) trustworthy and (second) almost obvious in its implications. Why did it strengthen her argument, in view of the possibilities that the system was inadequate to the specific task, and that on several occasions we imposed our ideas on the modeling system with its acquiescence but against its built-in principles?

## 2. Trust and Scientific Practice

When standards of scientific review are not to be applied thoroughly and objectively, what (how) do you trust? This question is by no means encountered only in modeling; rather the trust shown here is part of the ethos of science as practiced, as opposed to science as sometimes philosophized. Could it be that the model was credited out of deference to the specialist, a consequence of the unearned respect often given to experts in arcana? Is the rule that one may trust the modeler, not the model? Or could it be that modeling achieved a level of respect out of recognition of its successes, in drug

design, in mechanistic speculation, and in its guidance of experimental chemistry of many other kinds. I incline to the last explanation. It cannot be denied that in the past 15 years of physical organic chemistry, one has seen an overwhelming shift from physical measurement accompanied by occasional and ornamental calculations, to increasing emphasis on calculations of various kinds as aids in design and explanation, and sometimes, as the final arbiter of questions not easily addressed experimentally. This acceptance has grown because computer modeling systems can augment, extend, and improve the chemist's intuition.

We will certainly not bid farewell to the sketch or the ball-and-stick model, or the structural sketch. They were not equal to the task of helping us visualize the subtleties of the three-dimensional arrangements of atoms in the chiral Lewis acid catalyst and its participation in the Baylis-Hillman reaction or the Still-Wittig system's behavior in various media. However, they were capable of posing a question with enough precision that it could be delegated, to variable degree, to the repository of chemical judgment that is the modeling system. Our apprentices will not hesitate to turn to modeling the next time an argument needs buttressing, a speculation needs test, or a question seems beyond experimental reach.

*Warm thanks to Elva Van Divender and Scott Hart, for enduring.*

## Notes

- <sup>1</sup> Several types of models can be distinguished. We recognize first the iconic model which bears a physical resemblance to its object but is not called upon to function as its object does. Next in the hierarchy is the analogic model which may not resemble its object, but functions in a roughly equivalent way; and finally the abstract model which may share the logical structure of its object, but generally does not resemble nor function like the object. Linguistic representations, including mathematical and symbolic formulations and empirical verbal descriptions are abstract. We categorize the structural formula and quantum mechanical theory of molecules as abstract models while various objects including the ball-and-stick structure are iconic models.
- <sup>2</sup> Clearly the computer modeling software constructs an experience in which the abstract, iconic, and analogic aspects of modeling are all present. However the system succeeds or fails depending on the quality of the analogy it provides.
- <sup>3</sup> The sketch discussed above is certainly nothing like a structural formula. It is a more simplified representation of only a few aspects of the chemical system, in the spirit of the block diagrams introduced in studies of self-assembly or the more venerable cartoons representing secondary and tertiary structure of polypeptides *etc.*

- <sup>4</sup> For example the geometry of familiar HOH is explicitly modeled to produce bond angles close to the observed value of 105°, but the angle for O-La-O is defined as 180°, simply by the number of neighbors.

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