4. Chemical transforms

a) Fill in and extend transform library in heterocyclic and aromatic area
b) Develop interactive programs for update and maintenance of library
c) Explore additional methods for acquiring information from users
d) Expand capability to predict chemical reactivity from 3-D models

5. Evaluation

a) Develop forward-working simulator for plan evaluation
b) Evaluate feedback from users

C. METHODS OF PROCEDURE

Our current synthesis program (SECS-II) will serve as the foundation for future investigations in synthesis planning. It should be clear that the list of specific aims given above is not exhaustive, but illustrative, and is our view at this point in time. Each of these aims will now be discussed in more detail.

Symmetry. The most obvious need for symmetry is simply to prevent the generation of redundant precursors. Currently if SECS infers that cyclohexane could come from cyclohexene, since there are six single bonds that could be changed to a double bond, six cyclohexene precursors would be generated, then five would be deleted! Clearly it is more efficient to only produce one precursor in the first place, knowing that all bonds are equivalent. Work is underway to develop an efficient molecular symmetry recognizer, using graph theory and our representation of stereochemistry. The validity of this algorithm will have to be proven and tested. This symmetry information will then be incorporated into the various chemical transform applicator modules so that transforms are mapped onto the structure only in unique ways.

We also plan to use symmetry to constrain the generation of enantiomers since in some cases this needlessly doubles the number of intermediates generated. In the synthesis of racemic compounds, we treat enantiomers as being identical. Symmetry will be used in strategy to find ways to cleave the target into identical fragments, and also in a higher sense to prevent redundant strategies. Later we plan to investigate algoritms for detection of potential symmetry. While a general solution to this problem is not yet apparent, for certain classes of potential symmetry, the problem may be more tractible, e.g., when one must break one or more bonds to obtain a symmetrical structure. Symmetrical here means having more operators in its symmetry group than just the identity operator.

Model builder. Another goal is to improve the model builder (SYMIN) which calculates the minimum energy and optimum geometry of a chemical structure on the basis of classical mechanics. SYMIN should be generalized to handle more types of bonding, including hydrogen bonding, and electrostatic effects which are currently ignored. There is also a need to make it as efficient as possible. The symmetry information discussed above may be a useful heuristic in this regard. Other heuristics can also be used, e.g., recognizing appendages as units, staggering them and then moving them as a unit. Large appendages minimize slowly in the atom-by-atom algorithm. Another heuristic approach is to apply weighting factors to each atom so that in early stages peripheral atoms are free to move larger distances in each iteration. The numbering from our Stereochemically Extended Morgan Algorithm (SEMA) are an interesting set because they map a spanning tree onto the molecule with the origin of the tree usually corresponding to the center of gravity of the molecule.

It would also be useful if the chemist could impose general constraints on SYMIN to force the model to meet certain requirements. Ivan Sutherland's Sketchpad system had such general constraints but in a different problem area. These improvements to SYMIN would be useful to the DENDRAL CONGEN program and the PROPHET

pharmacology system, both of which use SYMIN, as well as to SECS.

Strategy and Planning. The simplest strategy is just to apply all transforms that fit--analogous to the chess legal move generator. This is a useful stragegy for exhaustively exploring a limited region of a problem, but normally it is desireable to constrain building the synthesis tree according to various other strategies. Unlike game playing, where a look-ahead can save one from making a bad move now, in SECS doing the look-ahead is the same as 'playing the move,' in that we have to do the expensive part--the chemistry--and there is no way of recovering the effort if it proves to be a fruitless direction. Deleting bad precursors is merely a way of hiding our mistakes.

A major area of interest is the development of heuristics to guide the search for simplification of the synthetic problem. Topological heuristics have already been implemented. We are now in a unique position to develop heuristics based on symmetry, stereochemistry, spatial orientation, strain energy and electronic factors. There are two important problems, 1) actually devising the heuristics and 2) actually implementing them in a synthetic program. Let us first examine the latter problem and then turn to what the heuristic might be like.

Rather than building strategies into the transforms as complex transforms consisting of preplanned sequences of subroutine calls (e.g., Corey's Diels Alder transform[11]), our approach is to try to cleanly separate strategy from transforms. We feel this is important to allow transforms to be added or updated without modifying the strategies and vice-versa. As the base of reactions increases, the importance of this separation becomes more obvious. A large library would be difficult to maintain otherwise. Another advantage of this approach is that goals can be ordered on merit rather than on the order of the statements in the transforms. Strategy modules will vote on strategic operations, e.g., breaking various bonds, or making certain bonds. The more votes a given goal has, the more powerful it becomes to demand subgoal creation. After all strategic modules have voted, the chemistry modules are passed once to satisfy these goals at a given level, rather than making multiple passes as is required when strategy modules directly call transforms.[14] This approach promises the least bias, the most creative results, but still controls the amount of output to within reasonable limits.

The planner will create short and long range plans, the latter extending over many levels of the synthesis tree, e.g.,"it is desired that a portion of the molecul remain untouched for most of the analysis." The chemist will be able to interact with the planner graphically or via teletype to modify or create additional plans.

Strategies based on Steric Effects. Steric congestion about a center can now be approximated by a function for ketones and olefins, and we hope to be able to extend it to SP^3 centers for oxidation, substitution, and elimination reactions. Congestion should be helpful in recognizing natural functional group selectivities, or adverse reactivities, and may help determine the priority for constructing stereocenters. Heuristics can be developed such as "work with the most accessible groups first, and later use the sterically congested ones." Sophisticated goals for reconnections and special blocking groups can be keyed by a need for greater congestio on one side of a reaction center.

Proximity is currently available from the 3-D model. Other proximity effects, e.g., anchimeric assistance, depend upon the orientation of a bond as well as the distance between groups. Proximity will also lead to recognition of differential reactivity and would key operations like congestion strategies.

Strategies based on Electronic perception. Currently the prime application is viewed as directing effects and relative reactivities on aromatic substrates. We currently have a molecular orbital module in SECS to provide needed perception. Related to this is the use of strain energy to trigger the need for mild irreversibl

synthetic methods. This also may focus attention on exactly what the trouble spots in a synthesis might be so that aspect may be dominant in planning.

Related to aromatic and heterocyclic systems is the problem that many different ring systems occur, all having different chemical properties. The use of HMO calculations eliminates the need for tables of data for each ring system. Of course there are limitations to the method, especially as the number of heteroatoms increases, but it provides a valuable heuristic in planning. More accurate evaluations can be applied once the synthetic routes of choice have been selected for refinement. More general strategies are needed however to determine when in a synthesis it is appropriate to work on the aromatic ring, and when it is appropriate to work on the remainder of the molecule. We are currently collecting data on this very question. Without this strategy, the behavior of the program is to jump around the molecule working here, then there, then here again, which is not the approach normally used in synthesis.

A graphical interface between the chemist and strategy module is planned to make the communication faster and more natural. There will still be complete capability also available from just a teletype for those users without CRT terminals.

Chemical Transforms. The ALCHEM libraries should be completed and extended in aromatic and heterocyclic chemistry. As the transform libraries continue to grow, finding out whether a certain reaction is present in the file becomes an increasing problem. Thus there is a need to develop programs for the maintenance and updating of the libraries, both to ease the problem mentioned and to assure consistency in the files. At the same time an interactive graphical interface to the chemist could be incorporated so he could inquire or enter a transform graphically. We would also like to generalize the ALCHEM representations so they could be used not only for the backward-working SECS, but also for retrieval and for a forward-working synthesis simulator.

The question arises of what SECS should do when a needed transformation isn't in the library. One approach is to let the chemist manually perform the transform at that stage in the analysis, then let SECS continue. SECS could remember that transform then, providing yet another way to extract information from users. Another approach is to let SECS revert to mechanistic generation at this gap to try to "invent" the desired transform.

In order to give transforms additional specificity based on our 3-D model, we plan to add to ALCHEM geometric descriptors defining lines, planes, angles, and other relationships. The arithmetic capability of ALCHEM would then allow manipulation and evaluation of these parameters. These capabilities will also be useful in representing biological reactions such as biosyntheses or metabolism. Other extensions to ALCHEM will include specification of short range "block avoidance", e.g., recognizing situations which prevent the use of a transform, automatically creating a subgoal to circumvent or correct the situation. This would be stated as IF . . . THEN CORRECT. If the situation could be corrected, the original transform would again be attempted, else it would fail. And finally, we will continue our research to correlate chemical structure and chemical reactivity as we have done with steric congestion.

Synthesis Plan Evaluation and Optimization. SECS is a planning program which works primarily backward and necessarily in generalities. It produces a synthetic plan (tree) with transform names, structures, and indications of protection and conditions. The next step is to develop a second program to perform the transforms in the forward direction, and evaluate factors more accurately than could SECS. It could also optimize reaction sequences, determine possible simultaneous steps and determine more accurately the requirements of protecting groups, when they must be introduced and removed. (Currently all that is specified is that the protecting group must be present in a particular step.)

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For the selected sequences, reactions and exact reagents would be specified, either by the chemist or by the program using a reaction data base. It could predict possible side products from the specified reaction, could retrieve appropriate literature references for experimental procedure, and even could label those structures in the tree that would be new compounds, not present in Chemical Abstracts Registry system.

Although the subprograms of SECS-II would be useful in the forward working program, the organization will be quite different. Ignoring the product shown in the synthesis tree obtained from SECS, the forward worker will attempt to predict the expected products, given the reactants and conditions. This involves finding reactions which can occur between the groups present under those conditions, estimating the relative extent of reaction and ratio of stereoisomers. It must of course consider both intra and inter-molecular reactions. The quality of the predictions will be dependent on the quality of the simulations and evaluation of the many factors involved. The description of the reaction mechanism would be in an ALCHEM-like language, but would view transforms from the side of reactants and conditions.

Evaluation by users. Feedback from users of SECS during this period will assist in improving the program, the approach, and in planning the research. Input of chemical transforms as well as intersting problems is expected from users. The number of users permitted and selection of them as well as the procedures involved will be worked out with the SUMEX-AIM community and administrators. It is also planned to explore other applications of SECS to demonstrate the generality of this program as a chemical problem solver. A specific problem of current interest is application in metabolism of drugs.

D. SIGNIFICANCE

This proposed research in computer-assisted biomolecular synthesis should enable investigators to plan more efficient syntheses faster, and with assurance that all the important routes have been considered in a methodical and unbiased way, using all reactions available. Consequently, the synthesis of molecules of importance to the national health care program should be achieved ultimately faster and at lower cost. This has direct bearing on the synthesis of drugs, labeled compounds for testing, and structure proof by synthesis. The many NIH grantees working on synthetic projects could gain access to this tool for assisting them in their own research program.

Further, the applications of advanced computer science to chemistry in this research has important implications for the solution of other important health-related problems involving molecular structure and man-machine communication. For example, molecular symmetry involving stereochemistry as we will find it would be required for prediction of C-13 or proton magnetic resonance spectra. Such symmetry information will be useful in generating all possible stereoisomers in the CONGEN structure generator program. The model builder is useful for generating geometries of molecules to predict spectra, or for biological activity comparison. That program is incorporated into the PROPHET pharmacology system now and would be improved by this research. And the SECS program itself may also prove useful in analysis of metabolism pathways which could be indicative of potentially dangerous metabolites of drugs or other foreign substances. Our concerns with managing a large growing data base are similar to those involved with medical diagnosis programs and drug prescription programs like MYCIN. Our analysis and evaluation of chemical reactivity from three-dimensional structure has potential applications in analysis of structures for biological activity according to shape, and has also importance in chemistry in understanding how reactions really occur and how reactic are sensitive to their environment. Lastly, our work in interactive computer

graphics has and will continue to establish techniques for efficient man-machine interaction which are useful to many other computer applications in medicine.

The significance of this research to the SUMEX-AIM community is that it provides an extended capability for dealing with biomolecular structures, for representing chemical transformations, and for evaluation of properties of biomolecules based on their graph theoretical and three-dimensional structure. This project will serve as an experiment for the feasibility of remote interactive graphics which is of interest to many SUMEX-AIM research projects. Our experience and research results will be available to all of the community, as well as our programs and algorithms. In this past six months of being a part of the SUMEX-AIM community, I believe this research has benefited from the dynamic interaction with other scientists interested in advanced computer science applied to medical problems. Our joint group meetings with the DENDRAL project at Stanford has been stimulating and hopefully will be able to continue. Already our model builder and graphics techniques have been adopted into SUMEX-AIM research programs of other investigators. I am sure there will be a continuing transfer and sharing of science and technology in the future.

SUMEX-AIM is very important to this research, for it is the only source of computing available which meets the needs for large interactive programs like SECS. Thus, this project as it is presently conceived is dependent on the availability of a large sophisticated timesharing system. Since there is none at Santa Cruz, access to the SUMEX system is important to the success of this research.

E. FACILITIES AVAILABLE

1 DEC GT40 graphics terminal
1 CDI model 1030 thermal printing terminal
1 9 trk high speed magnetic tape drive
IBM 360/40 computer (computer center)
500 square feet of space for this project, equipment and desks

F. COLLABORATIVE ARRANGEMENTS

As mentioned above, this project requires access to the SUMEX Resource at Stanford. The author is currently actively participating in the SUMEX Resource and has been for the past 6 months since he moved from Princeton to Santa Cruz. Currently SUMEX is providing computer time, disk space (4 K pages), one leased line, modems for that line, and TYMNET access. The author has discussed this proposal with NIH and with Dr. Joshua Lederberg, principal investigator of the SUMEX resource. The arrangements we have made are that this project would attempt to cover all terminal and communication costs, would provide a disk drive to increase the file space on SUMEX which is desperately needed, and SUMEX would provide an allocation of computer time and disk space for this research. A letter from Dr. Lederberg describing these negotiations is enclosed as Appendix 1.

G. PRINCIPAL INVESTIGATOR ASSURANCE

The undersigned agrees to accept responsibility for the scientific and technical conduct of the research project and for provision of required progress reports if a grant is awarded as a result of this application.

2 5 76 76 — Ted Wipke

Date — Principal Investigator

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STATEMENT FROM DR. J. LEDERBERG
PROFESSOR OF GENETICS AND
PRINCIPAL INVESTIGATOR: SUMEX-AIM COMPUTER RESOURCE

THIS NOTE IS IN RESPONSE TO THE OUTLINE OF THE OBJECTIVES OF DR. WIPKE'S PROPOSAL FOR A RESOURCE-RELATED RESEARCH PROJECT THAT APPEARS ON PAGE. 25. I HAVE ENJOYED TELEPHONE CONVERSATIONS WITH DR. WIPKE ON HIS PROPOSAL; BUT DID NOT HAVE THE ENTIRE TEXT AT HAND AT THE PRESENT TIME; I WILL BE HAPPY TO RESPOND IN MORE DETAIL TO HIS FORMAL PROPOSAL IF THERE ARE ANY FURTHER QUESTIONS ABOUT ITS RELATIONSHIP TO THE SUMEX AND DENDRAL PROJECTS BASED AT STANFORD.

DR. WIPKE'S WORK HAS BEEN ADJUDGED BY OUR ADVISORY COMMITTEE TO BE ONE OF THE MORE CREATIVE PROJECTS THAT BELONG TO THE SUMEX-AIM USER COMMUNITY. WE WELCOME THE AUGMENTATION OF THIS EFFORT THAT WOULD BE ENABLED BY THE SUCCESS OF HIS APPLICATION. SINCE HE MOVED TO UC/SANTA CRUZ AND BEGIN HIS WORK WITHIN THE SUMEX-AIM FRAMEWORK HE HAS ALSO DISTINGUISHED HIMSELF BY THE COOPERATIVE SPIRIT OF HIS EFFORTS AND HAS BEEN QUITE SUCCESSFUL IN RELATING TO THE CIRCLE OF INVESTIGATORS WORKING ON COMPLEMENTARY PROBLEMS HERE AT STANFORD. HIS ATTRIBUTIONS ABOUT THE COMPLEMENTARY ASPECTS OF HIS WORK; AND OF THE DENDRAL PROJECT; ARE IN ACCORD WITH OUR OWN PERCEPTIONS. WHILE WE HAVE HAD SOME OPPORTUNITY IN THE PAST TO TAKE ADVANTAGE OF HIS PARTICULAR CONTRIBUTIONS TO THE CALCULATION AND DISPLAY OF MOLECULAR GEOMETRIES; THE COOPERATIVE EFFORT WITHIN THE FRAMEWORK OF THE SUMEX-AIM RESOURCE HAS BEEN MUCH MORE EFFICIENT AND PRODUCTIVE. WE BELIEVE THAT OTHER USERS; E.G.; OF THE CONGEN PROGRAM; AND THE XRAY-STRUCTURAL ANALYSIS; WHO WORK ON SUMEX IN RELATED AREAS WILL CONTINUE TO BENEFIT IN A SIMILAR FASHION.

WE HAVE DISCUSSED THE RELEVANT DETAILS OF COST- AND RESOURCE-ALLOCATION WITH DR. WIPKE; AND BELIEVE WE HAVE AN EFFECTIVE ACCOMODATION AS SPELLED OUT IN HIS BUDGET JUSTIFICATION. SPECIFIC ALIQUOTS OF ACCESS TO THE SUMEX RESOURCE MUST BE RE-EXAMINED ANNUALLY BY OUR ADVISORY COMMITTEE; BUT THE LEVEL OF ENTHUSIASM FOR HIS WORK; TOGETHER WITH ACCUMULATING EVIDENCE OF THE COOPERATIVE STYLE OF HIS CURRENT EFFORTS LEAVE ME WITH NO DOUBT THAT HE WILL CONTINUE TO GET HIGH-PRIORITY APPROVAL WITHIN THE FRAMEWORK OF THE FAIR ALLOCATION OF THE RESOURCE TO ALL QUALIFIED USERS. THERE IS NO MANIFEST REASON FOR DR. WIPKE NOT TO RELY UPON SUMEX-AIM AS THE MEDIUM FOR HIS INVESTIGATIONS.

IN HIS OWN BUDGET HE HAS INDICATED THE AREAS WHERE INCREMENTAL CONTRIBUTIONS TO THE OPERATION OF SUMEX-AIM WOULD RELIEVE SERIOUS PRESSURES ON THE RESOURCE FOR THE SPECIFIC BENEFIT OF HIS OWN PROJECT.

THAT WAS MESSAGE 42

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