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(45) The wave function representing a state of the whole interacting system can be expanded into a linear combination of various electron configurations of reactants, belonging to the same irreducible representation of the point group. The 2 + 2 cycloaddition via a three-centered interaction followed by the rotation of a reactant, as proposed by the present authors, can be described by a wave function the dominant term of which is the closed-shell configuration. On the other hand, if the reaction proceeds through the charge transfer from the HOMO of donor to the LUMO of acceptor, retaining such a symmetry as is characterized by the definition "$2_s + 2_s$" by Woodward and Hoffmann, the ground state of the whole system should fall into an open shell in the regioselectivity-determining stage.
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(47) An alternative explanation has been given by Epiotis [footnote 17 in ref 9a]. It is interesting that the rotation in the acceptor molecule was observed in the case of the cis donor, but not in the case of the trans donor. The difference is also explicable on the basis of the three-centered geometry. This problem may be closely related to the orientation of the talling center in the acceptor. The tail atom may occupy the same side as the substituent of the donor with a lone pair, due to nonbonded attraction between the tail atom and the lone pair similarly coming from the HOMO–LUMO interaction.[48] The preferential orientation of the tail atom is expected to occur toward the trans donor and to fix the configuration on the tail atom. On the other hand, the neighboring substituent, an alkyl group, in the cis donor may hinder the similar orientation due to the steric interference.
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General Methods of Synthetic Analysis. Strategic Bond Disconnections for Bridged Polycyclic Structures

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Abstract: A general procedure has been developed for the analysis of bridged polycyclic molecular networks to identify those bond disconnections most apt to lead to synthetically accessible precursor structures. This procedure has been implemented in LHASA-10, the Harvard program for computer-assisted synthetic analysis, and it has been utilized in various ways for goal generation to guide antithetic operations. Examples are given to illustrate the use of the strategic bond method, its limitations, and possible refinement. An evaluation of the method based upon a comparison with current synthetic practice is presented. The techniques and strategies described herein are also relevant to human problem solving.

The strategy devised by a synthetic chemist for the construction of a complicated molecule is usually related specifically to particular aspects of the structure in question or to particular "key" chemical reactions which seem unusually suitable for the synthesis. Until recently[1] there has not been much concern for the development of more general strategies of synthesis which could be applied to a *wide range* of problems. Such strategies are operative at a higher level in the sense that they can assist in finding the "*ad hoc*" strategies which are restricted or tailored to an individual problem. One of the objectives of our project to devise a program for computer-assisted synthetic analysis has been the development of well-defined, *general* synthetic strategies[1a] and their testing to determine scope, power, and possible utility in the pedagogy and practice of synthetic chemistry.

Whether a problem-solving strategy is aimed at reducing the time and effort required to find a plausible solution or at the discovery of an unusually simple and effective solution, it may be characterized in terms of its position in a hierarchical collection of strategies, its objectives, its relationship to other strategies, its scope, its power, and its utility. Strategies for use in synthetic analysis by chemists may take the form of definite procedures or more flexible "guidelines". (In the extreme, the human intellect must even be capable of using subtle strategies of which it is not even consciously aware.) An example of a strict procedural (or algorithmic) strategy is the choice[1b] of a rigorously antithetic[1a] (retrosynthetic) mode of synthetic analysis.[2] An example of a more flexibly used strategy is the recognition of the merit of "convergence" [3] in a synthesis and the use of this as a "guideline" in the analysis of a particular problem. In this case the objective of the strategy is clear but, since the means of achieving that objective are not delineated, the application of the strategy is pragmatic.

The Harvard program for computer-assisted synthetic analysis (LHASA-10) is highly interactive and allows virtually unlimited input and decision making by the chemist-

user as an analysis progresses. However, central to the design of the program is the principle of using a variety of explicitly defined strategies,[1a] which can be used independently or in combination, to guide the search processes utilized by the machine "on its own". The program is rigorously antithetic and the strategies, which currently are selected by the program user,[4] vary from the straightforward use of matching operations[5,6] to select transforms[1a,6] which are applicable to a target structure either directly or through a small number of subgoals[6] (a very low-level, primitive strategy) to the use of multi-step look-ahead search strategies for transform selection and application.[1a,7]

Antithetic analysis in LHASA is guided by the paramount objective of simplifying molecular structure in terms of molecular size, functionality, internal connectivity (network), stereorelationships, and chiral centers, etc., so that simpler and simpler precursor structures can be derived. All LHASA strategies are based on this objective and involve either transform-oriented goals (for example, to apply a certain type of transform or a particular transform for molecular simplification) or structure-oriented goals. One of the most interesting strategies in the latter category is directed toward simplification of the molecular network by selective disconnection of those ring bonds which lead to the most accessible and/or simplest precursor structures. This strategy, which attempts to find the most "strategic" bond disconnections (or, simply, "strategic bonds"), has been implemented for ca. 4 years in LHASA. The report on this strategy in the present paper is prompted by its successful use in LHASA and by the observation that the goals and procedures involved are relevant to human problem solving as well. An outline of one of the early procedures for the perception of strategic bonds has been given elsewhere.[1a] The presentation which follows deals with the techniques currently (1974) used for the recognition and use of strategic bonds in LHASA and with possibilities for further extension of this concept.

Perception of Strategic Bonds. As indicated previously,[1a] the most desirable bond disconnections in the antithetic manipulation of structure are those in which the following structural features are minimized: (i) appendages, (ii) appendages carrying chiral centers, (iii) rings of medium or large size, and (iv) bridged rings. Ample justification of these "goals" is to be found in the body of knowledge now available on multi-step synthesis of polycyclic structures. Given the synthetic target structure **1**, for example, and considering just four of the possible bond disconnections, it is apparent that the structures **2**, **3**, **4**, and **5**, which are produced by cleavage of bonds a, b, c, and d, respectively, differ considerably in terms of synthetic accessibility (Figure 1). Since synthetic accessibility is not subject to rigorous mathematical definition, the techniques for the recognition of the most strategic disconnections have been derived heuristically. The rules used, which depend upon a combination of chemical and topological considerations, are outlined below. They are intended to apply primarily to bridged polycyclic networks. Additional details of the strategic bond selection procedure appear in Appendix I.

Rule 1. Because of the relative ease of formation of common-sized rings, a strategic bond must be in a four-, five-, six-, or seven-membered "primary" ring. *A primary ring is one which cannot be expressed as the envelope of two or more smaller rings bridged or fused to one another.* Thus,

6

the six-membered envelope ring of structure **6**, for example, is not a primary ring. We designate such rings as "*secondary*" *rings*. Rule 1 is restricted to primary rings because, in general, the progress of a synthetic ring-forming reaction is affected strongly by the size of the *smallest* ring containing the bond being formed when the new bond is shared by two or more newly formed rings.

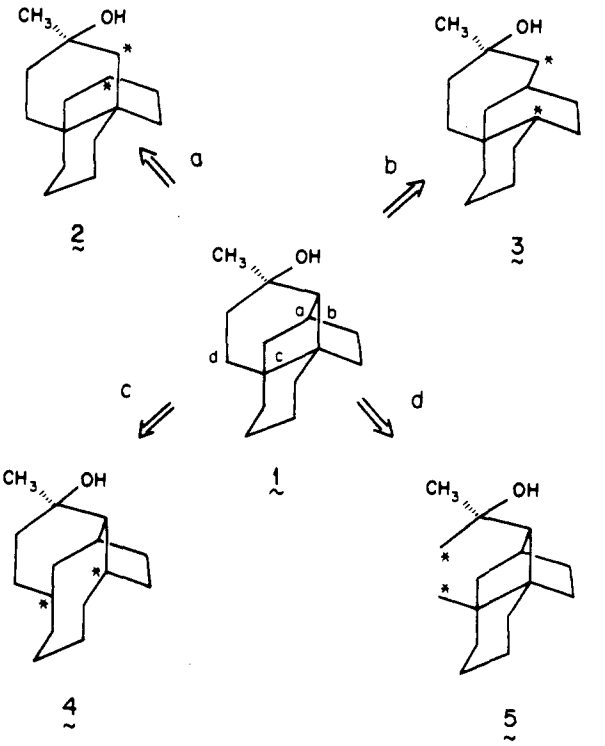
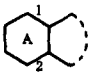


Figure 1. Cyclic systems which result from the cleavage of bonds a–d in **1**.

Rule 2. A. A strategic bond must be directly attached to another ring (exo to another ring) since very commonly, in synthesis, a ring disconnection which produces two functionalized appendages leads to a more complex overall synthetic route than a ring dissection which leads to one or no functionalized appendages. This procedure therefore leads to the generation of offspring structures in which the number of appendages on rings is minimized. According to this



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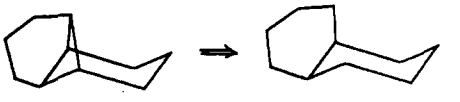
rule, of the six bonds in ring A of structure **7**, only bonds 1 and 2 can be strategic.

B. Due to the paucity of ring closure methods in which bonds are formed to preexisting three-membered rings, strategic bonds may not be exo to rings of that size. This condition in effect limits the range of application of part A.

Rule 3. To achieve maximal simplification of the cyclic system, strategic bonds should be in the ring (or rings) which exhibits the greatest degree of bridging. For example, in the ring system **8**, the centrally located four-membered ring is the maximum bridging ring. Disconnection of any bond in that ring produces a major network simplification

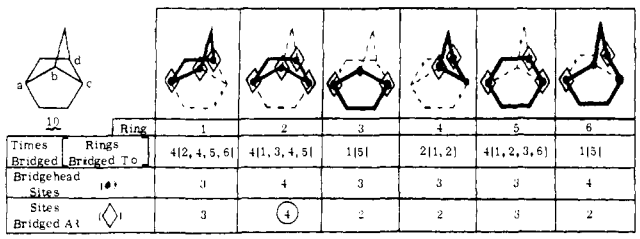


8 9

to a decalin structure (**9**). The maximum bridging ring (or rings) is selected from the set of "synthetically significant rings", which is defined as *the set of all primary rings* (see

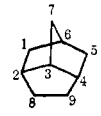
rule 1) *plus all secondary rings less than eight membered.*[8]

The maximum bridging rings of a molecule are defined as those rings which *are bridged* at the *greatest number* of sites. This definition is *not* equivalent to defining maximal bridging rings as those *containing* the greatest number of bridgehead sites, *nor* is it equivalent to defining them as the rings which are bridged *most* to other rings. The subtle differences among these definitions are exemplified in the maximum bridging analysis of structure **10** shown below.



Of the six synthetically significant rings comprising structure **10** (primary rings 1–4 and secondary rings 5 and 6), ring 2 is bridged at more sites (four) than any other ring and hence is defined as the maximal bridging ring. Ring 6, which contains as many bridgehead sites as ring 2, is not a maximal bridging ring since it itself is bridged to other rings only at two of these sites (a and d). The above analysis further shows that the number of times a ring is bridged is not a valid criterion for determining maximal bridging character. For example, although ring 5 of structure **10** is bridged by as many other rings as ring 2, it is not a maximal bridging ring since it is bridged at one less site than ring 2.

For consistency, we define an atom to be a bridgehead if it appears in the following topological context. If two intersecting synthetically significant rings have more than one consecutive bond in common, then the atom at each end of the common path is considered a bridgehead.[9] In structure **11,** for example, the two primary five-membered rings 1-



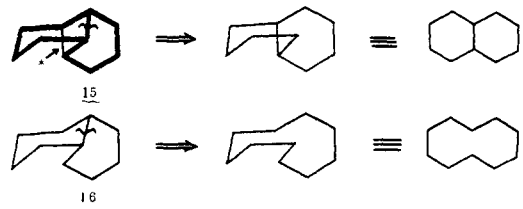
11

2-3-7-6 and 3-4-5-6-7 contain the common path 3-7-6. Atoms 3 and 6 are therefore bridgehead atoms. The intersection of primary ring 2-3-4-9-8 and synthetically significant secondary ring 1-2-3-4-5-6 reveals a common path described by atoms 2-3-4. Atoms 2 and 4 are therefore also bridgehead atoms.

Rule 4. To avoid the formation of rings having greater than seven members during antithetic bond cleavage, any bond common to a *pair* of bridged or fused primary rings whose envelope is eight-membered or larger cannot be considered strategic. The bonds which are eliminated from further consideration by this rule are termed "core bonds". All bonds in the cyclic network which are *not* core bonds are candidates for strategic bond designation and are termed "perimeter bonds". Thus, in the example of decalin (**13**),

13 14

the centrally located darkened bond is a core bond since its cleavage would lead to the formation (antithetically) of a ten-membered ring (**14**). The remaining bonds in **13** are perimeter bonds. An important exception to this rule is taken whenever the two fused or bridged rings being examined are *directly* joined elsewhere by another bond. In structure **15,** for example, the bond located at the fusion of the two darkened six-membered rings would appear to be a core bond. However, closer examination reveals that its cleavage would



15

16

not produce a new ten-membered ring since the two six-membered rings are directly connected by another bond (starred). Thus, the fusion bond is still a candidate for strategic bond designation. On the other hand, in the absence of the connecting bond, as in **16,** the fusion bond must be treated as a core bond.[10]

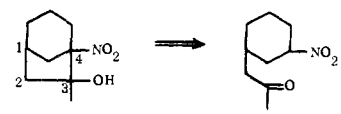
Rule 5. Bonds within aromatic rings are not considered to have potential strategic character.

Rule 6. A. If a cyclic arc linking a pair of common atoms (i.e., fusion atoms, bridgeheads, or spiro ring junction atoms) contains a chiral carbon atom, then none of the bonds in the cyclic arc may be considered strategic. Thus those cleavages which would leave stereocenters on side chains are avoided. In structure **18,** for example, atoms 1 and 4 are common atoms. Breaking any of the bonds on the

18 19

1,2,3,4 arc would produce a structure in which chiral carbon 3 is on a side chain (such as **19**). In general such a situation is undesirable since the synthetic introduction of chiral centers in chains is much less subject to stereochemical control than for centers in rings.

B. This part effectively modifies the operation of part A for the special case of bonds *directly attached* to a chiral center, when that is the *only* chiral center on the arc linking the two common atoms. Such bonds are not excluded from the set of possible strategic bonds since their disconnection can remove chirality at the atom in question and hence need not lead to undesirable chirality in the newly generated side



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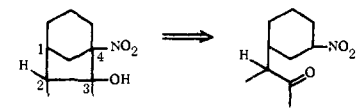
chain. In structure **20,** for example, disconnection of bond 3-4 to the chiral atom 3 leads to a side chain without chiral atoms. This exception to part A cannot be made when an arc between common atoms contains more than one chiral center. In **21,** for example, cleavage of bond 3-4 now leaves chiral atom 2 on a side chain.



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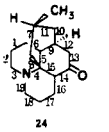
Application of Rules 1–6 to Carbocyclic Networks. The set of strategic bonds in a carbocyclic network is determined by taking the intersection of the collections of bonds which satisfy each of the six rules outlined above; that is, a

Table I. Identification of Strategic Bonds

(a) Sample structure (lycopodine, **24**) with arbitrary bond numbering



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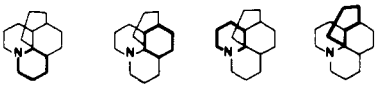
(b) Primary rings



(c) No synthetically significant (<eight-membered) secondary rings

(d) Bridgehead atoms

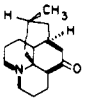
(e) Strategic bond determination: carbocyclic procedure

	Bond Number (Using Numbering Indicated in (a))																		
Rule 1:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Rule 2:	–	–	3	4	5	6	–	8	9	10	--	12	--	14	15	16	--	--	19
Rule 3:	–	–	–	–	5	–	–	8	9	10	--	12	13	14	15	--	--	--	--
Rule 4:	1	2	3	–	–	6	7	8	–	10	11	12	13	14	--	16	17	18	19
Rule 5:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Rule 6:	1	2	3	4	5	6	7	–	9	--	11	12	13	14	15	16	17	18	19

(f) Strategic bond determination: C–heterobond procedure

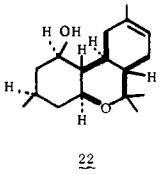
	Bond Number																		
C–N bonds:	–	–	3	4	–	–	–	–	–	--	--	--	--	--	--	--	--	--	19
Rule 2B:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Rule 4:	1	2	3	–	–	6	7	8	–	10	11	12	13	14	--	16	17	18	19
Rule 5:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Rule 6:	1	2	3	4	5	6	7	–	9	--	11	12	13	14	15	16	17	18	19

(g) Strategic bonds: bonds 3, 12, 14, 19



strategic bond must satisfy all the rules.

The C-Heterobond Procedure. Complex ring systems containing heteroatoms such as O, S, or N cannot be examined satisfactorily for strategic bond disconnections solely using rules 1-6 which embody no consideration of the rich and powerful chemistry for forming bonds between carbon and these heteroatoms. Therefore, a modified selection is followed for heterocyclic networks. To the set of strategic bonds determined by application of rules 1-6 above is added the collection of bonds in the cyclic network between carbon and O, N, and S which satisfy rules 2B, 4, 5, and 6. For example, the five darkened bonds in **22** are determined to be strategic by rules 1 to 6. The C-heterobond procedure defines additionally as strategic the two bonds indicated in



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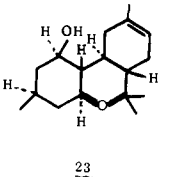
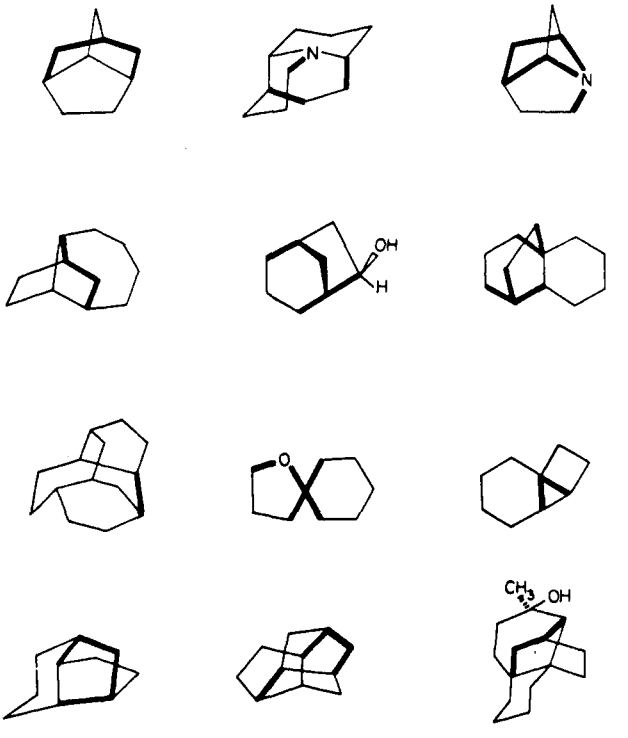


23

23, one of which is already included in **22**, and a new bond, previously eliminated by rule 2. The final set of strategic bonds identified for this structure is therefore the six bonds darkened in **22** and **23**.

The results of the application of the rules for strategic bond perception to other cyclic systems are pictured in Tables I and II. Table I provides a step-by-step summary of the strategic bond identification process for the tetracyclic molecule, lycopodine, while Table II illustrates the bonds perceived as strategic (darkened bonds) in 12 other polycyclic systems.

Table II. Strategic Bonds in Sample Polycyclic Systems



Strategic Bond-Based Chemistry in LHASA. The automatic identification of strategic bonds in polycyclic structures leads immediately to a number of effective techniques for synthetic problem solving, several of which are em-

ployed by current versions of LHASA. These "strategies" are guided by the following generalized procedure.

(1) The set of strategic bonds in a polycyclic target or intermediate structure[11] is determined according to the steps outlined in the preceding sections.

(2) The antithetic cleavage of a member of the strategic bond set is adopted as a "goal".

(3) For the strategic bond disconnection goal assigned in step 2, a determination is made of the structural obstacles which prevent the *direct* application of a transform which will satisfy the goal (i.e., cleave the strategic bond).

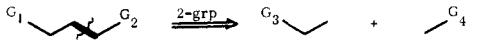
(4) If obstacles are found to exist, an antithetic sequence is developed to remove each obstacle, in stepwise fashion, until the structural environment of the strategic bond matches the requirements of at least one of a number of transforms, for example, "two-group" or "one-group" type,[1a,6,12] which can then operate in the *next antithetic step* to cleave the strategic bond.

(5) The procedure is repeated for each strategic bond in the structure.

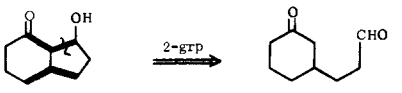
The intermediate structural modification steps (points 3 and 4) which operate to set up the molecule for strategic bond disconnection are termed "subgoals". Transforms which are applied as subgoals generally cause no overall structural simplication and, in some cases, may actually render the target compound temporarily *more* complex. Thus, such processes are only applied to a compound by LHASA when it is clear that, by their application, an otherwise blocked, simplifying transform (goal) will be allowed to operate on the current target. Previous publications[1a,6] have dealt with the use of functional group interchange (FGI)[6] transforms and functional group addition (FGA)[6] transforms as *subgoals* leading to the application of two-group disconnective transforms and major ring disconnection[7] processes.[13,14] In the case of ring transforms,[7] LHASA may develop subgoal sequences consisting of as many as 15 individual steps. However, in the current implementation of strategic bond-oriented chemistry, LHASA restricts the subgoal search to four steps. If a strategic bond cannot be disconnected using four or fewer steps, the search is terminated and a different strategic bond is examined.

(a) Application of Disconnective Two-Group Transforms as "Goals". After identifying all strategic bonds in the current target, LHASA enters a processing phase in which the molecule is examined according to the following steps.

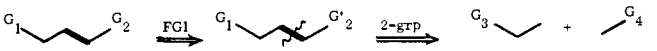
(1) LHASA selects for application to the target those two-group transforms which will break a strategic bond. In the schematic representation G_1 and G_2 are the functional



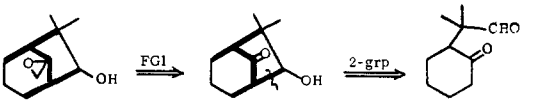
groups in the target which match the requirements of a transform in the two-group transform library.[6] If the bond which will be broken by the transform is also a strategic bond (darkened bond), the transform is accepted for further evaluation, otherwise it is rejected, e.g.



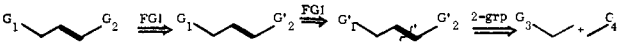
(2) If one of the groups, for example G_2, does not match the requirements of a transform in the two-group library, a functional group interchange (FGI) subgoal is generated to



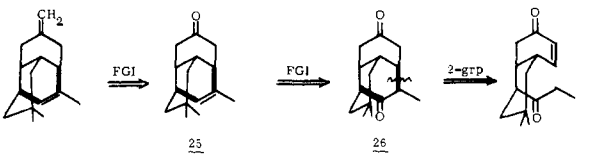
convert G_2 to G'_2 so that, on the next analysis level, the strategic bond can be broken, e.g.:



(3) LHASA then enters a processing stage which focuses on those strategic bonds in the molecule which could not be disconnected directly by a two-group transform (as in step 1 above) nor be set up for eventual cleavage by application of a one-step FGI subgoal (as in step 2 above). In this stage, several approaches are considered. The first of these is a parallel double FGI consisting of two subgoals, the conversion of each of the groups G_1 and G_2 to a group pair which



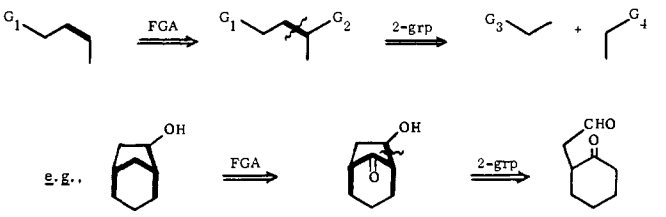
enables the selection of one of a small collection of important two-group transforms[16] for strategic bond disconnection. The following example is illustrative of the performance of such a process in LHASA. During the execution, the transformation of **25** to **26** was automatically assigned a



lower than normal "rating," [6] since it was recognized that interference by the standby carbonyl group in **26** would necessitate a protection-deprotection operation. LHASA also "flagged" the interfering carbonyl group with a graphical indicator to bring the conflict to the chemist's attention.[17]

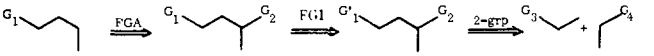
(4) If the strategic bond is still unbroken, an attempt is made to obtain a match to the group pair required by one of four powerful disconnective transforms using a sequence of 2, 3, or 4 FGI's on one of the groups.[18]

(5) The parallel double FGI form of subgoal sequence generally can be applied only if two functional groups are situated reasonably close together and on opposite sides of a strategic bond. If a second group is absent,[19] a functional group addition (FGA) is attempted to insert a group at an

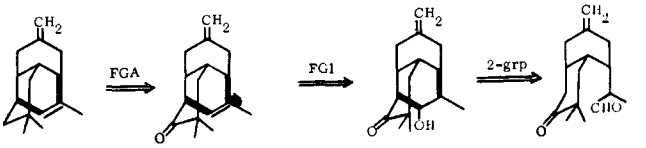


appropriate distance from the strategic bond.[20]

(6) If the FGA subgoal still does not form a match for one of the allowed two-group transforms, an FGI is applied to the first functional group in an attempt to complete the match.



This type of two-step subgoal is a combined FGI/FGA, and is exemplified below:



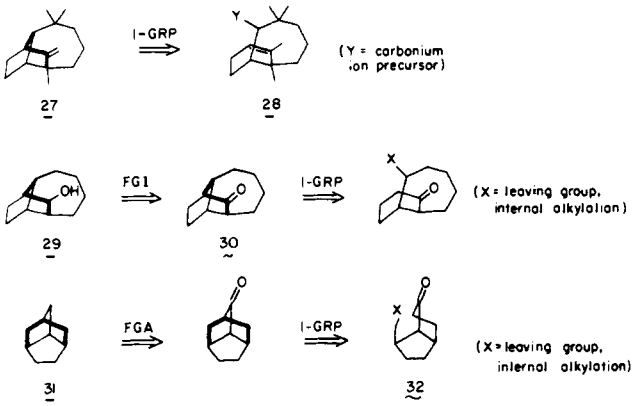
In this example, as in that pictured in step 3 above, the development of a two-step subgoal sequence allows the discon-

nection of a strategic bond which results in a major simplification of the cyclic network.

(7) If a strategic bond cannot be opened successfully, even after the generation of a multi-step subgoal sequence, it is bypassed, and the next unbroken strategic bond is processed. Once all the strategic bonds have been examined in this manner, control of the analysis is returned to the user.

(b) One-Group Transforms as "Goals". Procedures for the cleavage of strategic bonds by the application of one-group transforms operate according to the same principles as outlined for the two-group case. The search for subgoal transforms which lead to the application of a one-group "goal" is, however, considerably less complicated, since only a single functional group is involved in the subgoal sequence. In fact, in the strategic bond-oriented one-group approach, there is no opportunity to apply sequences such as the parallel FGI or combined FGI/FGA described above. Only single-step FGI's or FGA's are attempted.

In the one-group strategic bond-based analysis mode, LHASA first selects all one-group transforms which will result in the cleavage of a strategic bond (e.g., **27** to **28**). Each strategic bond which could not be disconnected directly is then subjected to a detailed examination in which, if possible, a single step FGI is employed (e.g., **29** to **30**) to convert a nearby functional group to a group which matches the requirements of one of a set of four or five major one-group processes. The strategic bond may then be disconnected on the next analysis level by the direct operation of the



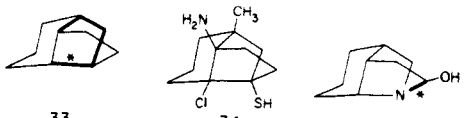
matched one-group transform. If in the region surrounding the strategic bond a functional group is not available for FGI conversion, one or more FGA subgoals are attempted,[21] again, to match the requirements of a one-group transform (e.g., **31** to **32**). Thus, even with target molecules which contain no functionality, LHASA is able to perform effective functional group-based analyses.

The current version of LHASA provides an additional strategic bond-based analysis option which the chemist may apply to a cyclic target. In this mode, *both* the two-group and one-group approaches discussed above are brought to bear on the problem of strategic bond disconnection. As each subgoal is generated, a record is kept of the "name" of the goal transform which caused the subgoal to be invoked, so that, in a final pass before returning control to the user, LHASA automatically disconnects the strategic bonds by direct application of a two-group or one-group transform. No manual intervention is required in the process.

Discussion

The presentation of the strategic bond approach outlined in the preceding sections calls for serious consideration of its limitations and scope, its logical refinement and extension, and its use in human problem solving as well as machine analysis. We shall deal briefly with all of these matters in the following discussion.

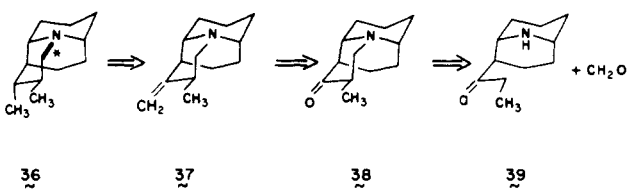
Especially with regard to the first item, it should be stated at the outset that, as with all strategies, the strategic bond approach is by no means universally successful. Indeed, knowledge of the approach brings with it the capability of designing situations where the approach is bound to fail.[22] For example, starting with skeleton **33** with strategic bonds as shown, it is possible to devise structure **34** for



which none of the bond disconnections indicated in **33** are very attractive simply because functionality has been introduced which rules out these disconnections or makes others more likely to succeed.[23] On the other hand, in structure **35**, the rules are quite adequate despite the dramatic alteration due to the introduction of a carbinol amine function since the heterobond extension procedure defines a new and highly important disconnection (as shown).

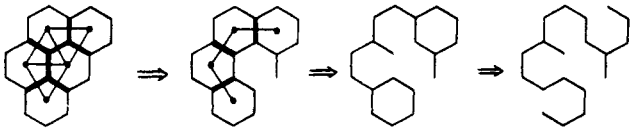
In keeping with the awareness that there are limits to the scope of the strategic bond procedure and also with the philosophy of LHASA as a highly interactive program intended to *optimize the man-machine combination*, LHASA will accept from the user a manual designation of strategic bonds. The chemist using LHASA may add to or remove from the computer-chosen strategic bond set one or more strategic bonds simply by activating a graphical control button[5,24] and pointing to each of the bonds. The program then attempts to disconnect the manually designated strategic bonds as it would those which are determined by the automatic procedure. The manual technique plays a role, therefore, in enlarging the scope of the strategic disconnection approach. For the chemist, the opportunity of manual selection adds an experimental and enjoyable dimension to the use of LHASA.

Another apparent limitation on the effectiveness of the strategic bond selection rules is indicated by the consideration of **36** as a target structure. The starred bond in **36** would not be perceived as a strategic bond because of rule 6 which is intended to prevent disconnections which leave chiral centers on side chains. As a consequence, the strategic bond approach per se would not contribute to the generation of precursors **37–39.** This situation is not as disastrous as it might seem for the following reasons. LHASA maintains a record of the chiral atom-bearing arcs which prevent a bond from being designated strategic because of rule 6. If this information is now used *to direct the application of transforms which can remove the offending chiral centers or to disconnect the ring to form an appendage devoid of chiral centers*, a powerful new strategy results. Thus, from the limitations of the strategy, new obstacle-removing strategies are constructable, an example of the nested or hierarchical strategic relationships mentioned in the introduction.[25]



The rules described herein for the generation of strategic bond disconnections were designed specifically for *bridged*

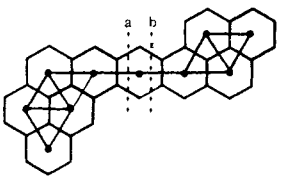
polycyclic networks and are not particularly appropriate for polycyclic *fused* ring structures. However, a simple technique has been devised (though not yet implemented in LHASA) to guide the disconnection of fused ring structures in the direction of simpler ring systems and/or chains with minimum occurrence of branches and/or appendages. This method can be illustrated readily by a few simple examples. Expression **40** depicts a pentacyclic fused ring system and also its *dual* in the graph theoretic sense.[26,27] The darkened bonds represent "core" bonds as defined above. A strategic cleavage of the molecule can be effected as follows: (1) Select that ring which has the largest number of core bonds and at least one noncore bond. Disconnect a *non*core bond in that ring which is exo to the adjacent ring (e.g., converts **40** to **41**). (2) Repeat procedure 1 if necessary until the resulting dual is linear. (3) Disconnect each *non*core bond which is exo to two rings (e.g., converts **41** to **42**). (4) Disconnect each bond endo to terminal rings at connecting chain (e.g., converts **42** to **43**). The intermediates so obtained, e.g., **41, 42,** and **43,** are then targets for further synthetic analysis. To this procedure may be added constraints such as those against disconnections which result in chiral centers on newly generated chains (rule 6) and extensions for heteroatoms as described above for bridged ring systems. Procedure 1-4 converts **44** to the linear acyclic structure **45,** from which it is clear that this approach to the disconnection of fused ring systems can be used in conjunction with search procedures[7] for the application of ring transforms such as cation-olefin cyclization or Robinson polyannulation to find especially direct synthetic pathways.



40 41 42 43

44 45

In the case of polycyclic structures such as **46** for which the corresponding dual consists of linearly connected cycles,



46

a highly advantageous disconnection is that of procedure 5 which separates the cycles of the dual by cleaving the ring with vertex of order two with the breaking of the bonds exo to the adjacent ring(s) (disconnections a and b). The fragments so obtained (which correspond to the intermediates of a convergent synthesis[3]) can then be treated by procedure 1-4.

The above procedure for the systematic dissection of fused polycyclic systems provides helpful direction for synthetic analysis. However, the degree to which it is successful in a given case will depend considerably upon the structure in question, especially with regard to functionality and stereochemistry.

Not infrequently, cyclic structures may be greatly simplified by the disconnection of *pairs* of bonds within the same *primary* or *secondary* ring. Such disconnections are, of course, outside the scope of the strategic bond procedure described above. Despite this fact, the limitation is of no significance in LHASA, since simplifying disconnections of bond pairs are found by another (and more suitable) approach, namely the use of multistep look-ahead search procedures[7] to apply important ring transforms which operate on bond pairs, e.g., the Diels-Alder, 2 + 2 cycloaddition, and 2 + 1 cycloaddition transforms.

Perhaps the major limitation on the effectiveness of the strategic treatment outlined here is encountered in the analysis of very highly bridged, very complex polycyclic structures (more complex than the most highly bridged known natural product). This topic is currently under study with the view of extending the present methodology to include even such cases.

Of the several possible ways of evaluating the effectiveness of the strategic bond approach as outlined herein, one of the simplest and clearest is the comparison of the bond disconnections which it selects for a range of polycyclic bridged structures with synthetic routes which have actually been demonstrated by experiment. For purposes of making such a comparison here, we have selected the group of outstanding syntheses collected together in ref 28. Fourteen of the syntheses in this collection involve target molecules of the bridged polycyclic type. For ten of these cases (aspidospermine, copaene, helminthosporal, ibogamine, longifolene, lycopodine, morphine, quinine, strychnine, and twistane), the strategic bond procedure correctly identifies bond disconnections corresponding to those involved in the demonstrated synthesis. One synthesis (ajmaline) deviates from the rules only in that one of the disconnections was carried out leaving a stereocenter on a side chain instead of removing that chiral center before disconnection. (It is noteworthy in this case that the synthesis was *not stereoselective* with regard to the actual generation of that stereocenter, thereby providing a vindication of the rules.) Two of the syntheses (astarane and patchouli alcohol) followed routes not generated by the strategic bond approach, but which involve bond-pair disconnecting transforms (2 + 1 cycloaddition and 4 + 2 cycloaddition). These synthetic routes are readily derived by LHASA using its ring transform oriented look-ahead strategy.[7] One synthesis (α-caryophyllene alcohol) falls outside the range of either strategic bond or bond-pair disconnection and involves the conversion of the bridged target structure antithetically to a fused ring system by a Wagner-Meerwein rearrangement transform. The existence of this synthesis, a rather special case, simply points up the need of a transform-oriented strategy for the rearrangement of rings *prior* to disconnection. Such a strategy is not currently in LHASA but is an obvious candidate for future addition.

The result of this comparison is quite favorable to the strategic bond selection procedure. It is also quite consistent with evaluations made on the basis of other synthetic problems and on accumulated problem-solving experience with LHASA.

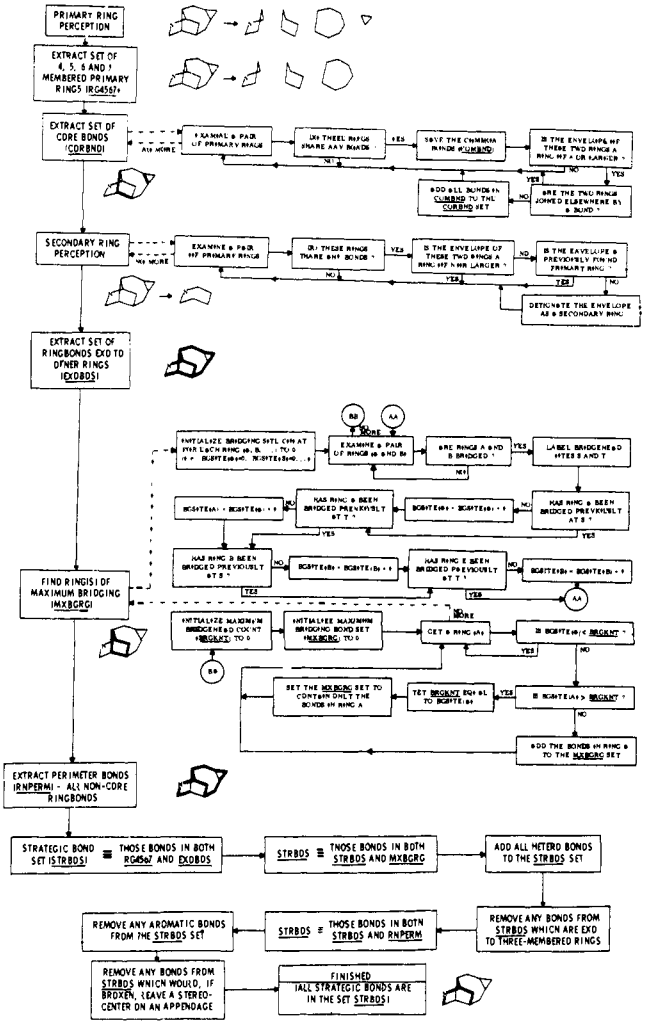
We close with a few observations on the utility of network analysis of the type considered herein in regard to human problem solving. In our experience, the technique is valuable in synthetic planning if learned well and applied carefully. It would not be surprising if the strategic bond method evolves into an even more powerful tool with additional use and experience, or if it serves as a forerunner of other general problem solving procedures which can well serve the practice and teaching of molecular synthesis.

Acknowledgment. We are indebted to the U.S. National Institutes of Health for a grant in support of this research.

The application of strategic bond perception to transform selection in LHASA-10 was largely carried out by Mr. William Jorgensen, to whom we are much indebted.

Appendix I

The following flow chart summarizes the strategic bond selection process currently implemented in LHASA. Certain computationally complicated processes which are conceptually simple for humans, such as the perception of primary rings[29] and the identification of bonds with aromatic character,[30] are not delineated. In all other respects, however, the following algorithm is complete and can be used for manual derivation of the strategic bonds chosen by LHASA.



Supplementary Material Available. Appendix II, a listing of the program for strategic bond perception, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.00 for microfiche, referring to code number JACS-75-6116.

References and Notes

(1) See, for example, (a) E. J. Corey, *Q. Rev., Chem. Soc.*, **25**, 455 (1971); (b) *Pure Appl. Chem.*, **14**, 19 (1967); (c) E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Am. Chem. Soc.*, **86**, 478 (1964).

(2) Clearly this strategy also would occupy a very high level in the hierarchy of all strategies. It is very general, but in a sense of only modest power, since it is not highly restrictive of the problem-solving search.

(3) L. Velluz, J. Valls, and G. Nomine, *Angew. Chem., Int. Ed. Engl.*, **4**, 181 (1965).

(4) Strategy-selecting strategies, though not yet implemented in LHASA, are planned for the program in the future.

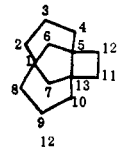
(5) E. J. Corey and W. T. Wipke, *Science*, **166**, 178 (1969).

(6) E. J. Corey, R. D. Cramer, III, and W. J. Howe, *J. Am. Chem. Soc.*, **94**, 440 (1972).

(7) E. J. Corey, W. J. Howe, and D. A. Pensak, *J. Am. Chem. Soc.*, **96**, 7724 (1974).

(8) Secondary rings which are included in the set of "synthetically significant" rings are those which can be formed from a *pair* of smaller primary rings.

(9) However, if the two atoms at the ends of the common path are *directly connected* by another bond, they are not considered bridgehead atoms. In hypothetical structure **12**, for example, intersecting rings 5-13-11-12 and 1-7-13-11-12-5-6 contain the common path 5-12-11-13. Atoms 5 and 13, at the ends of the path, are not bridgehead atoms since they are directly joined by the 5-13 bond. This, however, does not eliminate them from further consideration since the bridging intersection of the five-membered ring with each of the two six-membered rings reveals that atoms 1, 5, and 13 are bridgehead atoms.



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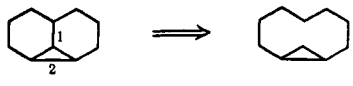
(10) In structures of type **17**, this heuristic breaks down since the presence of bond 2 allows bond 1 to be considered as a perimeter bond (candidate for strategic bond designation) when, in fact, cleavage of bond 1 *does* produce a ring of undesirable size. The overall procedure of strategic bond selection is not compromised, however, since bond 1 would be rejected by one of the other rules (see part B of rule 2).



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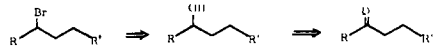
(11) The collection of antithetic pathways which are developed from the overall target molecule forms a branching structure called the "synthetic tree".[5,6] The nodes of the tree correspond to synthetic intermediates, each of which may be treated as a target and processed further.

(12) "One-group" transforms are those whose application to a target substructure is keyed by the presence of a *single* functional group.[6] Members of this class are exemplified by the Wittig transform (keyed by a double bond, the "product" group of the Wittig reaction), or the Grignard transform (keyed by a hydroxyl group). "Two-group" transforms[6] are keyed by a particular *pairing* of functional groups which are separated by a specific number of carbon atoms, such as the aldol transform, which is keyed by a carbonyl oxygen and hydroxyl separated by three carbon atoms.

(13) A single functional group interchange (FGI) transform may suffice to convert the functional group in the target structure (subject group) to the required (object) group, but a multiple FGI sequence may be necessary, for example:



FGI sequences of up to four FGI's may be found in the current version of LHASA.

(14) Functional group addition transforms (FGA's) result in the *insertion* of a functional group where none existed before, such as in A → B. This

corresponds to the complete *removal* of a group in the synthetic direction. Since application of FGA's results in an increase in molecular complexity, transforms of this type are applied only when such action will clear the way for a major simplification of the structure.

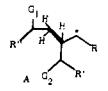
(15) All transforms which are candidates for application to a current target molecule (including FGI and FGA subgoal transforms) are subjected to a detailed evaluation procedure[6] to determine the likelihood that the *corresponding synthetic reaction* will proceed in reasonable yield in the laboratory. Transforms which pass the evaluation step are then applied to the current target to generate an offspring structure.

(16) Only six of the more than 150 two-group transforms in LHASA's library are considered to have sufficient synthetic utility to merit treatment as "goals" in the strategic bond-based development of sequential and parallel FGI, single FGA, and combination of FGI/FGA subgoal sequences. This restriction has the twofold effect of simplifying the subgoal selection process and of preventing the uncontrolled addition to the synthetic tree of large numbers of sequences with questionable synthetic utility.

(17) A detailed treatment of the subject of functional group reactivities, reaction conditions, competitive reactions, functional group protection, and the strategies used by LHASA in dealing with these important considerations will be presented in a forthcoming paper (E. J. Corey, H. W. Orf, and D. A. Pensak, *J. Am. Chem. Soc.*, in press).

(18) The algorithm used for this procedure will be described in a subsequent paper (E. J. Corey and W. L. Jorgensen, *J. Am. Chem. Soc.*, in press).

(19) Whenever possible, an FGI subgoal will be attempted before an FGA. Thus, in A, for example, if the strategic bond cannot be broken by the direct application of a two-group transform, single FGI's will be attempted on G_1 and G_2 in turn. If this is still not successful, a double parallel FGI or a multiple sequential FGI will be attempted. Only if a proper



match still cannot be formed will an FGA subgoal be attempted at the starred carbon.

(20) The "appropriate distance" will, of course, depend on the nature of the particular goal transform toward which the subgoal sequence is leading. Since there is no a priori selection of *one* of the five or six candidate two-group transforms as a goal, several retrosynthetic pathways are generally developed which lead to several different ways to open a given strategic bond.

(21) Several different types of functional groups may be inserted since there are several different goal transforms which may be employed to cleave strategic bonds. Also, the atom to which the new group is attached will generally be one, two, or three atoms away from the strategic bond, depending on the type of group being inserted and, by extension, the nature of the goal transform being cleared by the subgoal. On the average, four or five antithetic routes are developed to break each strategic bond. Again, before any subgoal transform is applied to a molecule, it is subjected to a detailed evaluation step.[6]

(22) There is some analogy to the state of affairs in a contest in which knowledge of a strategy allows the foiling of that strategy.

(23) Nonetheless the strategic bond rules work well for the majority of structures based on **33**, and the cleavage of the starred bond in **33** guides the analysis toward an elegant and demonstrated synthetic plan; see J. E. McMurry, *J. Am. Chem. Soc.*, **90**, 6821 (1968).

(24) E. J. Corey, W. T. Wipke, R. D. Cramer, III, and W. J. Howe, *J. Am. Chem. Soc.*, **94**, 421 (1972).

(25) A search procedure guided by the strategy of chiral-center removal is currently being implemented in LHASA.

(26) "Given a plane graph *G*, *its geometric dual G** is constructed as follows: place a vertex in each region" (= chemical ring) "and, if two regions have an edge *x* in common, join the corresponding vertices by an edge *x** crossing only *x*." See F. Harary, "Graph Theory", Addison-Wesley, Reading, Mass., 1969, p 113.

(27) Arbitrarily all rings are depicted as six membered.

(28) N. Anand, J. S. Bindra, and S. Ranganathan, "Art in Organic Synthesis", Holden-Day, San Francisco, Calif., 1970.

(29) The perception of primary rings in LHASA is accomplished by means of a straightforward "spanning tree" algorithm. See K. Paton, *Commun. ACM*, **12**, 514 (1969).

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Probing of the Interrelationship between Heteroatomic Substitution and Equilibrium Imbalance in 2,8-Trimethylenesemibullvalene Derivatives[1]

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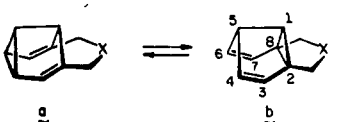
Abstract: To assess the magnitude and direction of equilibrium caused by certain electronegative atoms, three 2,8-annulated semibullvalenes have been synthesized. These molecules are directly patterned in structure after the 2,8-trimethylene bridged hydrocarbon which was known to exhibit approximately equal partiality for the two valence tautomeric forms at room temperature. For the three cases where the central methylene group was replaced in turn by O, S, and $NCH_2C_6H_5$, the equilibrium was shifted substantially in that direction where the cyclopropane ring occupies a central position in the molecule. The level of this imbalance was found to vary somewhat depending upon the particular hetero atom. The ^1H NMR spectra of the oxa- and thiasemibullvalenes show little temperature dependence in the range -120 to $+100°$. This feature suggests that entropy factors control the isomer distribution. Thus, although the hetero atoms are not bonded directly to the fluxional system, measurable ground state effects of significant magnitude are clearly in evidence.

Few, if any, organic molecules can be expected to attain the facility for Cope rearrangement which prevails in semibullvalenes.[4-6] This hydrocarbon ring system contains a *cis*-1,2-divinylcyclopropane moiety which is rigidly constrained into a folded conformation. The resulting cant of the internal cyclopropane σ orbital in relation to the two peripheral π bonds is such that electronic realignment in the [3.3]sigmatropic mode requires minimal activation energy.

Because valence isomerization in **1** is doubly degenerate,[7] there cannot exist a weighted thermodynamic preference

1a **1b**

for one of the two structures. Consequently, perturbational effects arising from framework substitution of semibullvalene should be directly assessable without added complication. This novel feature has commanded recent theoretical[8,9] and experimental attention.[10-12] For monosubstituted semibullvalenes, variable temperature ^1H NMR studies have denoted preferential bonding to olefinic > cyclopropyl > aliphatic carbon, irrespective of the location and nature of the R group.[10,11] The response to bracketing effects is recognized to be more delicate.[5,12] For example, 2,8-bridging with a trimethylene chain to give **2** seemingly stabilizes the pair of tautomers almost equally, **2b** being favored to the extent of only 57% at $+40°$. Equal distribution of the two isomers exists at $-29°$ (CS_2 solution) and **2a** dominates the equilibrium below this temperature. For the tetramethylene case (**3**), only limited spectral changes are noted throughout a wide temperature range. Valence tautomer **3a** is substantially favored under these conditions. As concerns **4**, a preference for **4a** (58%) exists at $+40°$ (CS_2 solution); in the vicinity of $+17°$, however, crossover occurs and **4b** is favored at the lower temperatures. The responses of **2** and **4** to changing temperature are therefore diametrically opposite. The causative factors are of course due to the varying importance of the $\Delta H°$ and $T\Delta S°$ terms to the individual equilibria.[12]



2, X = CH_2
3, X = CH_2CH_2
4, X = $(CH_2)_3$

Because the semibullvalene nucleus serves particularly well as a fine-tuning device for the probing of ground state perturbational effects, a detailed systematic investigation of