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Computer Assisted Graph Theoretical Analysis of Complex Mechanistic Problems in Polycyclic Hydrocarbons. The Mechanism of Diamantane Formation from Various Pentacyclotetradecanes

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Received May 16, 1974

Abstract: The pentacyclotetradecane rearrangement graph culminating in diamantane (**1**) has been analyzed. The most probable mechanistic pathways from tetrahydro-Binor-S (**2** or **3**), hydrogenated Katz [2 + 4] norbornadiene dimers (**7** and **8**), and [2 + 2] norbornene dimers (**9**, **10**, and **11**) were deduced by graphical analysis guided by empirical force field (strain) calculations. Graphs of isomeric hydrocarbons were generated from a chosen precursor by 1,2-alkyl shifts, employing the simulation and evaluation of chemical synthesis (SECS) computer program. Due to the extremely large number of possible intermediates, it was necessary to simplify graph generation by adopting certain assumptions. From a given hydrocarbon precursor, all possible 1,2-shift isomers were generated and their strain energies calculated. The resulting isomer with lowest energy was processed further. Graph generation proceeded in this manner until diamantane was reached. The most probable mechanism for isomerization of **2** or **3** → **1** is proposed to involve, in sequence, *trans*-pentacyclo-$[8.2.1.1^{2,5}.0^{3,7}.0^{8,12}]$tetradecane (**6**), a tetrasubstituted intermediate (**24**), **28**, and protodiamantane (**29**). In the actual reaction, **6** was found to be the last isolable intermediate, as predicted by the strain energy calculations. When structures with tetrasubstituted cations were excluded from the graph, sets of interconverting pentacyclotetradecane isomers were obtained. The sets considered were derived from the [2 + 2] norbnene dimer **11** (6 structures), from the [2 + 4] hydrogenated Katz norbornadiene dimer **7** (10 structures), from tetrahydro-Binor-S (**2**) (13 structures), from **28** (293 structures, designated family [1,2,4] [3,5,6]), and from diamantane (**1**) (119 structures, family [1,3,5] [2,4,6]). Experimentally, isomerization to the lowest energy isomer within each family prior to further reaction *via* tetrasubstituted intermediates appears to take place, and the yield of diamantane decreases with the number of family boundaries which must be crossed.

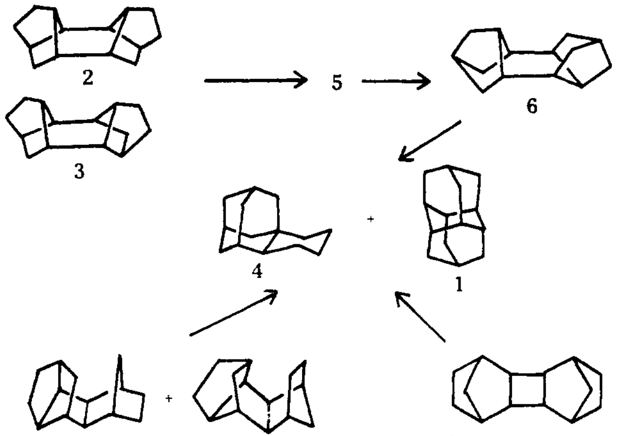
Lewis acid catalyzed isomerizations of hydrocarbons are complex, thermodynamically controlled carbocation processes.[2] Skeletal transformations, *e.g.*, that giving adamantane,[2b] involve hydride abstractions and multiple Wagner-Meerwein rearrangements. Since the number of possible intermediates and reaction pathways may be astronomically large, the determination of the detailed mechanism can be exceedingly difficult.

Such complex systems require systematic analysis. The first pertinent approach appears to be that of Balaban, Farcasiu, and Banica,[3] who developed a graphical treatment interrelating all structures interconvertible by 1,2 shifts, which allowed calculation of the number of possible isomers and pathways. For hypothetically labeled ethyl cations, automerization, *e.g.*, $H_1H_2H_3C_1{-}^{+}C_2H_4H_5 \rightleftarrows H_4H_5C_1{}^{+}{-}C_2H_3H_2H_1$, etc., involves 20 possible classical cations interconvertible by 30 1,2 shifts. The propyl cations are similarly interconverted with a possible intermediacy of 1680 isomers and 3150 pathways. Application of this approach to larger, nondegenerate systems is, however, extensively complex unless assumptions reducing the number of isomers and pathways are made.

Whitlock and Siefken[4] analyzed the possible mechanisms for adamantane formation from *endo*-tetrahydrodicyclopentadiene and other tricyclodecanes by means of a similar graphical method. A graph was generated by assuming all possible 1,2-alkyl shifts. Simplification was achieved (1) by considering only hydrocarbons and omitting cations from the graph, (2) by excluding all highly strained structures, *e.g.*, those containing three- and four-membered rings, and (3) by excluding structures formed from primary cation intermediates, *e.g.*, alkyl substituted isomers. A chemical graph containing 16 $C_{10}H_{16}$ tricyclodecane isomers resulted. By actual count, 2897 different pathways for interconversion of *endo*-tetrahydrodicyclopentadiene to adamantane were possible!

Structures containing small rings or alkyl groups would be high in energy and unlikely to be formed in appreciable amounts under the thermodynamically controlled reaction conditions. By extension of this argument, structures lowest in energy are likely to be formed in the largest amounts and are most likely to lie on the actual pathway. Employing computer conformational analyses, Engler, Farcasiu, Sevin, Cense, and Schleyer[5] calculated the strain energies not only for the hydrocarbons in the Whitlock graph but also for the related cation intermediates. Highly strained structures as well as highly exothermic pathways were eliminated as being improbable. This technique enabled the prediction of the most probable mechanistic pathway for the rearrangement of *endo*-tetrahydrodicyclopentadiene to adamantane.[5] The available experimental evidence is consistent with this pathway.

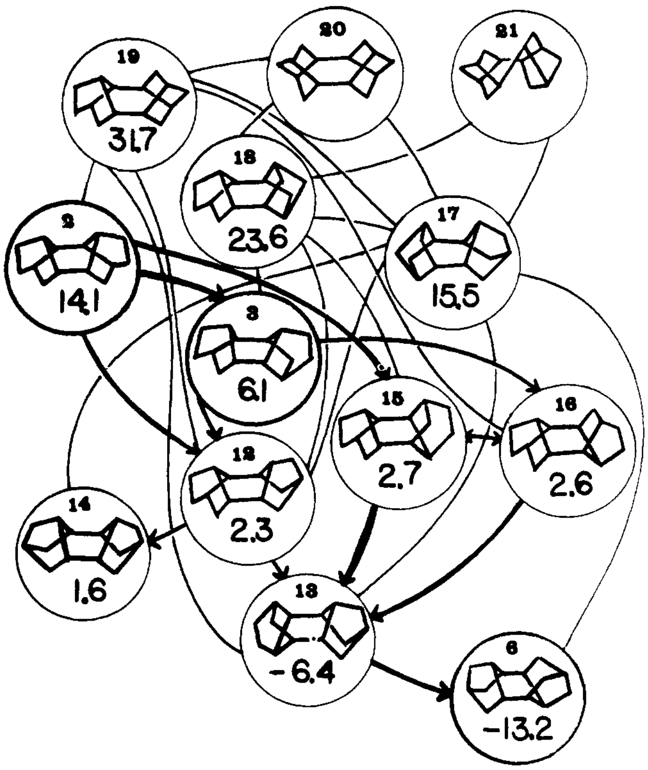
The determination of the mechanism of diamantane formation from various pentacyclotetradecanes is particularly challenging. Experimentally, the yield and smoothness of isomerization varies with the structure of the precursor. Tetrahydro-Binor-S (**2** or **3**)[6] isomerizes to diamantane (**1**) with remarkable ease in about 70% yield.[6,7] At 0°, the reaction proceeds with formation of two major (maximum concentration of each 20%) and at least five minor (less than 1%) intermediates. At the end of the reaction, however, only diamantane (**1**) and a disproportionation product (**4**)[6] remain. The initial intermediate (**5**), which has not been identified, isomerizes to the major intermediate identified (largely by ^{13}C nmr) as *trans*-pentacyclo[8.2.1.1^{2,5}.0^{3,7}.0^{8,12}]tetradecane (**6**).[6b] **6** then slowly (within several hours) rearranges to **1**. Hydrogenated Katz dimers, a 7:1 mixture of **7** and **8**, and the [2 + 2] norbornene dimers, a mixture of **9**, **10**, and **11**, isomerize less readily and give more complex reaction mixtures. The major reaction in these cases appears to be disproportionation to form by-product **4**; diamantane (**1**) is obtained in 25% yield from the **7**–**8** mixture and in 1–10% from precursors **9**, **10**, and/or **11**.[6]



9-*exo*-trans-*exo*
10-*exo*-trans-*endo*
11-*endo*-trans-*endo*

The application of the same graphical approach to the diamantane rearrangement is complicated by the enormous number of possible intermediates. We have estimated that there are at least 40,000 pentacyclotetradecanes;[8] connecting even a small fraction of these isomers by 1,2 shifts would give myriad interconversion pathways.

Chart I. Tetrahydro-Binor-S Graph[a]



[a] The graph was generated by excluding tetrasubstituted isomers. Bold numbers on top of each figure designate the compound, while the values underneath each structure are calculated heats of formation (kcal/mol); *cf.* ref 19. Darkened arrows indicate the energetically most probable pathways; lines indicate other possible interconversions. The ordinate of the graph is approximately proportional to calculated heats of formation, with the more strained isomers at the top.

A computer assisted graphical approach which involves the generation of a map of interconverting isomers and pathways could greatly aid in the solving of such complex mechanisms. Whitlock and Siefken[4] pointed out that their method of graph generation was ideally suited to computer processing, and recently Collins and Johnson[9] reported a very specific computer program which enumerates all of the intermediates and interconversion pathways through which substituted bicyclo[2.2.1]heptyl cations can undergo rearrangement.

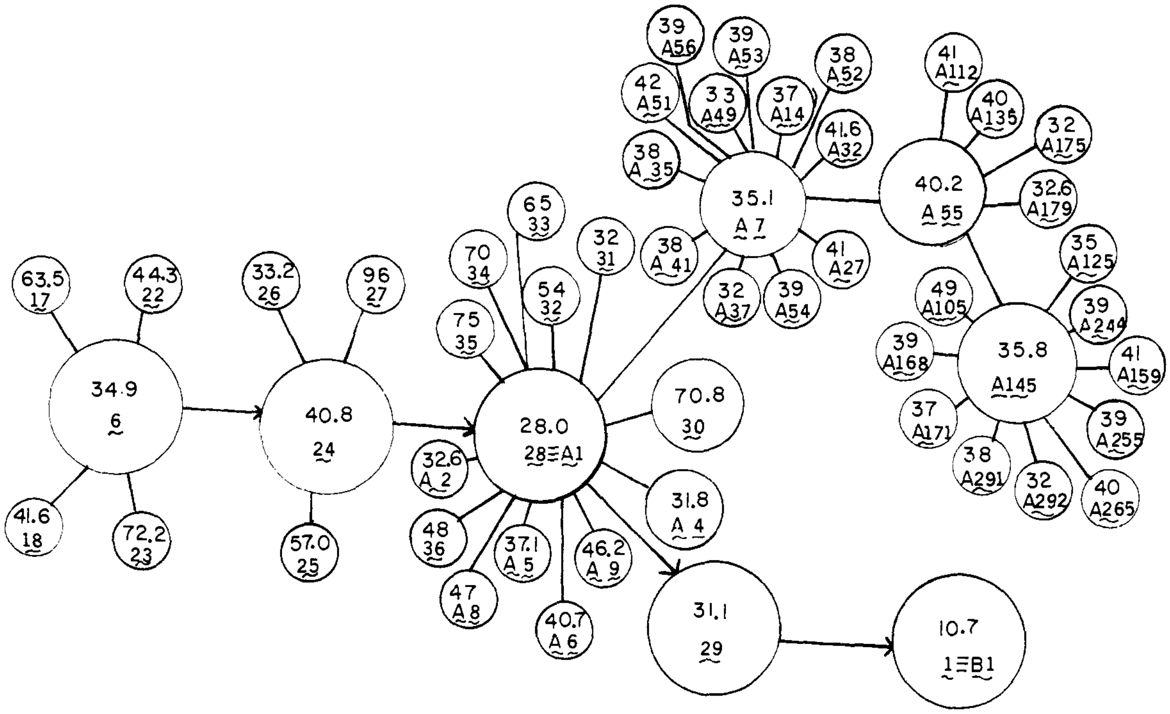
At Princeton, the simulation and evaluation of chemical synthesis (SECS)[10-17] program is able to generate structures according to the chemist's specifications. Furthermore, the SECS model builder SYMIN[10-17] calculates the three-dimensional structures, atom coordinates, and rough strain energies quickly; these may then be refined by the more accurate computer conformational analysis (empirical force field) calculations.[18,19]

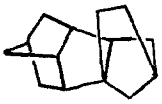
These programs were than applied to study the possible mechanisms of rearrangement of pentacyclotetradecanes **2**, **3**, and **7**–**11** to diamantane (**1**). Low energy pathways were discovered which appear to be quite plausible. The novel computer-assisted graphical method which was developed can be applied generally to study very complex rearrangement mechanisms.

Derivation of Mechanism

Our first goal was to derive a reasonable mechanism for the rearrangement of tetrahydro-Binor-S (**2** or **3**) to diamantane (**1**). Not being aware at first of the actual complexities involved, we started to solve this problem using Whitlock and Siefken's[4] graphical approach. After generating over 350 unique structures manually with no end in sight, it became obvious that additional assumptions were necessary. The difficulty with such manual generation of

Chart II. Generated Graph[a,b]

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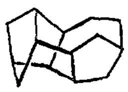
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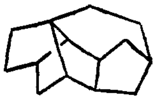
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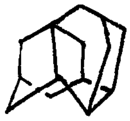
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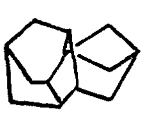
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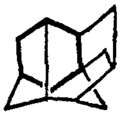
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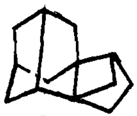
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[a] Illustrates the method of graph generation, the most likely rearrangement pathway from **6**, and one tributary from **28**. [b] Underlined numbers designate compounds. The other values are calculated strain energies in kcal/mol; those given to one decimal point were obtained by use of the full force field (ref 19) while those given to two significant figures are approximate strain energies obtained by the SECS Model Builder SYMIN program, ref 10-17. Table I compares strain energies calculated by the two programs. Circles represent structures which can be found in Figures 1, 2, and 3 and throughout the text. Lines connect structures interconvertible by single 1,2-alkyl migrations; bold lines with arrows indicate most likely pathways. (Structure with tetrasubstituted carbons are omitted from the generation from A7.)

structures lies in the fact that each new structure must be compared to all previously generated pentacyclotetradecanes to eliminate duplicates and identify all possible pathways. Visual recognition of duplicate $C_{14}H_{20}$ structures is difficult, tedious, and prone to error as illustrated in Figure 1, which shows five different projections of the same structure, each slightly turned.[20]

We postulated that, due to geometrical constraints in pentacyclic systems containing only 14 carbons, $C_{14}H_{20}$ isomers containing quaternary carbons should have relatively high strain energy and therefore were less likely to intervene during rearrangement. (This assumption was supported by strain calculations.) To test this hypothesis, we generated a graph by 1,2 shifts starting from **2** excluding the formation of tetrasubstituted structures. Chart I, containing 13 tetrahydro-Binor-S isomers resulted, but this did not lead to diamantane. The isolated diamantane intermediate, *trans*-pentacyclo[8.2.1.1^{2,5}.0^{3,7}.0^{8,12}]tetradecane (**6**), was indicated by empirical force field (strain) calculations to be the lowest energy isomer. Isomerization proceeding readily to **6** is, indeed, observed experimentally.[6b] Interestingly, **6** also is isolated from the hydride transfer reaction of Binor-S with sulfuric acid-methylcyclohexane.[6b] **6** Isomerizes to diamantane by aluminum bromide without any observable intermediates.

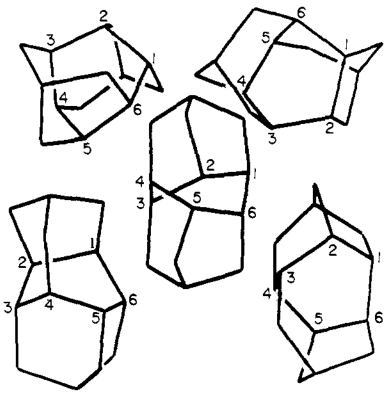


Figure 1. Five projections of structure **28** ≡ **A1**.

Table I. Comparison of Calculated Strain Energies (Heats of Formation) by Empirical Force Field and SECS Model Builder (SYMIN) Programs (kcal/mol)

Family	Hydrocarbon	Molecular mechanics[a] strain (ΔH_f)	SYMIN[b] strain
[1,3,5] [2,4,6]	**1** ≡ **1B**	10.69 (−37.37)	0.5
	37	23.64 (−24.42)	15.3
	38	25.68 (−22.38)	20.7
Tetrahydro-Binor-S	**2**	62.16 (14.10)	55.6
	3	54.15 (6.09)	48.6
	6	34.85 (−13.21)	38.5
[1,2,3] [4,5,6]	**12**	50.33 (2.27)	47.6
	13	41.64 (−6.42)	39.7
	14	49.61 (1.55)	55.9
	15	50.74 (2.68)	40.4
	16	50.70 (2.64)	41.1
	17	63.51 (15.45)	46.9
	18	71.65 (23.59)	52.2
	19	79.72 (31.66)	58.2
	20		83.5
	21		82.0
Tetrasubstituted	**22**	44.33 (−4.84)	51.6
	23	72.21 (23.04)	57.0
	24	40.80 (−8.37)	43.1
		40.52 (−9.02)[c]	
	26	33.19 (−15.98)	42.1
	29	31.05 (−18.12)	26.8
	30	70.80 (21.63)	52.5
	31		32.2
[1,2,4] [3,5,6]	**28** ≡ **A1**	28.00 (−20.06)	25.4
		28.10 (−20.28)[c]	
	A4	31.78 (−16.28)	29.3
	A7	35.05 (−13.01)	22.9
	A9	46.24 (−1.82)	38.4
	A6	40.71 (−7.35)	39.2
	A2	32.51 (−15.55)	40.4
	A5	37.10 (−10.96)	40.2
	A55	39.13 (−8.93)	19.9
	A145	35.84 (−12.22)	24.9
Hydrogenated Katz (2 + 4) norbornadiene dimers	**7**	49.77 (1.71)	50.4
	8	57.15 (9.09)	52.0
	39	39.57 (−8.49)	47.5
	40	40.61 (−7.45)	47.4
	41	48.25 (0.19)	46.9
	42	57.89 (9.83)	52.3
	43	65.25 (17.19)	52.1
	45	46.06 (−2.00)	49.4
	46	46.75 (−1.31)	46.8
(2 + 2) Norbornene dimer	**9**	57.62 (9.56)	80.5
	10	62.57 (14.51)	80.5
	11	68.03 (19.97)	72.6

[a] Reference 19. [b] Approximate strain energies; see text for discussion. [c] Our calculations are based on Allinger's force field, ref 18b.

Since the graph in Chart I essentially ends at **6**, at least one tetrasubstituted intermediate must be involved on the route to diamantane, and this intermediate must be of higher energy since **6** is isolable. In the analogous *endo*-tetrahydrodicyclopentadiene to adamantane rearrangement, two tetrasubstituted intermediates are thought to be involved.[4]

To continue graph generation from **6**, tetrasubstituted intermediates are required; however, generating a full graph is highly impractical. To solve this problem, we formulated the following approach which no longer considers all the possibilities but generates only those portions of the graph which are energetically favorable. Starting with **6**, hydrocarbon isomers were generated by 1,2 shifts (explicit consideration of the carbocation intermediates were omitted for the time being). Strain energies for the generated isomers revealed the best candidates for the next intermediate. From the various possibilities the isomer lowest in strain was processed further and the same procedure was continued until diamantane was reached. In other cases, where the desired goal is not reached by such procedures, one must go back to the last choice point and process isomers of next to lowest energy. The generated graph illustrating the method is given in Chart II. Strain energies calculated by both programs are summarized in Table I. Thus, **6** gave three new isomers with tetrasubstituted carbon atoms, **22–24**, of which **24** was lowest in strain energy. Similarly, **24** gave four new isomers, the least strained of which was **28**. In the same manner **28** led, *via* **29**, to diamantane (**1**). Other energetically feasible structures (Chart II) do not lead to diamantane as readily. Isomerization proceeding by alternate routes, *e.g.*, **28** → A-**7** → A-**55** → A-**145** (Chart II), would go through less favorable higher energy structures. Chart II summarizes our analysis of pathways starting from **6**, illustrating the exploration of one such "dead-end" tributary.

The several most likely exothermic pathways for interconversion of tetrahydro-Binor-S (**2**) to *trans*-pentacyclo[8.2.1.1^{2,5}.0^{3,7}.0^{8,12}]tetradecane (**6**) are represented by the darkened arrows in Chart I. At least two intermediate hydrocarbons must be involved, but several isomers of comparable energy (**12**, **15**, **16**) may intervene. Eventually isomerization must funnel through **13** to **6**. The low energy isomer **14** appears to fall on a dead-end pathway and, once formed, may temporarily build in concentration before reverting back through **12** and **13** to **6**. Structure **14** is a good possibility for the experimentally detected product **5**, which is formed somewhat faster than **6** (Chart I).

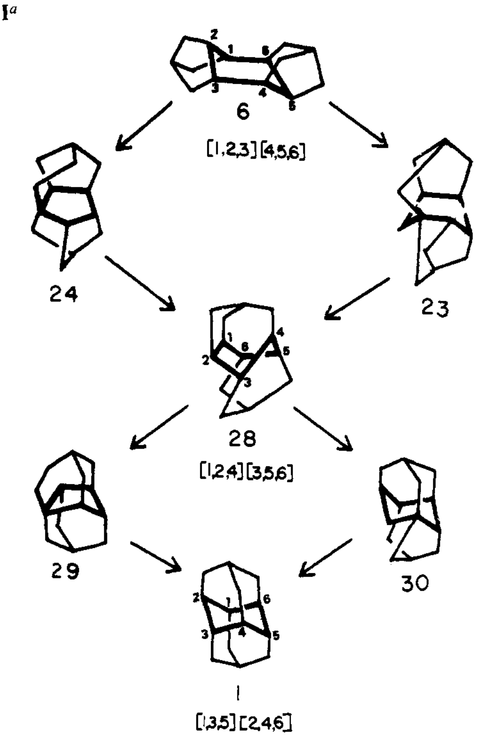
$$\begin{array}{lccccccccc} \Delta H_f^\circ(\text{calcd}), & \mathbf{6} & \longrightarrow & \mathbf{24} & \longrightarrow & \mathbf{28} & \longrightarrow & \mathbf{29} & \longrightarrow & \mathbf{1} \\ \text{kcal/mol} & -13.21 & & -8.37 & & -20.06 & & -18.12 & & -37.37 \end{array} \quad (1)$$

The proposed route from **6** to **1** (eq 1) is not only energetically favorable but efficient, involving only four isomerizations, two of which (**6** → **24** and **28** → **29**) are calculated to be endothermic by 4.8 and 2 kcal/mol and two of which (**24** → **28** and **29** → **1**) are exothermic by 11.7 and 19.3 kcal/mol, respectively (Chart II). These calculations suggest the rate determining step to be formation of **24**; the experimental results agree since past this point no other major intermediates were observed. Our analysis thus indicates that intermediate **28** should form during the rearrangement and is the lowest energy structure obtained from **23**, **25**, **26**, and **27** (Chart II).

In the above proposed route, the chair cyclohexane (darkened) in **6** becomes the middle chair cyclohexane (darkened) in diamantane. Throughout the rearrangement, alternation between six- and five-membered rings takes place, but the middle ring carbons need not become scrambled (Chart III). The three other mechanistic routes in Chart III would also produce this interesting result. For any of these routes, the reordering of methylene attachments around the central cyclohexane rings in **6**, **28**, and **1** (Chart III) can be envisioned to occur most easily by tetrasubstituted intermediates. In **6**, the attachments to the middle cyclohexane ring on one side are at positions [1,2,3] and on the other side at [4,5,6]; in **1** these attachments alternate, being at [1,3,5] on one side and at [2,4,6] on the other. These provide convenient designations of families of related isomers (see below).

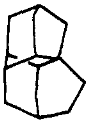
Formation of **1** must involve one of the four possible protodiamantanes (eq 2) as the penultimate intermediate. Both tetrasubstituted isomers (**29** and **30**) provide a direct route to **1** from **28**; however, **30** is much higher in energy. The other two protodiamantanes (**37** and **38**) are somewhat lower in energy but rearrangement of **2**/**3** through either **37** or **38** would involve one of the less favorable routes from **28**; eventually diamantane would be found *via* some higher en-

Chart III[a]



[a] Mechanistic pathways which ultimately preserve the chair cyclohexane ring carbons of **6**. Numbers in brackets designate methylene attachments above and below the darkened cyclohexane rings. See text for discussion.

ergy tetrasubstituted hydrocarbon. In agreement with the proposed mechanism, but not requiring it, the recently prepared protodiamantane **29** is readily isomerized with aluminum bromide to diamantane.[21]



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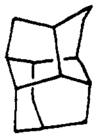

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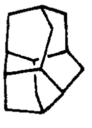

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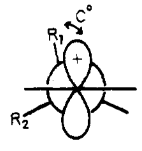
(2)

Consideration of Cationic Intermediates. Our topological treatment generates hydrocarbon structures only, while the actual process involves 1,2 cationic rearrangements *via* secondary and tertiary carbonium ions. The facility of these rearrangements appears to be governed by (1) the energy of the cationic intermediate and (2) the stereochemical orientation of the empty p orbital with respect to the migrating group. Rearrangements should be most facile when the vacant orbital and the C–R bond (where R is the migrating group) are coplanar, *i.e.*, when the dihedral angle is 0°.[22]



R_1 should migrate preferentially to R_2

Although it would be desirable to calculate the heats of formation of all cations, we assumed that the strains of secondary ions are proportional to those of the corresponding hydrocarbons.[5] Therefore, the strain energies of only the key tertiary carbocations, 6^+, $28a^+$, $28b^+$, and 1^+ on the proposed, mechanistic pathway were explicitly calculated (Table II). Carbocations 6^+, $28a^+$, and $28b^+$, although higher in energy than the known 1^+ or 1-adamantyl cation (Table II), should be accessible. The corresponding hydrocarbons, **6** and **28**, are more strained than **1** or adamantane; however, the difference in strain energy between the cation and corresponding hydrocarbon (Δ strain) of 6^+, $28a^+$, and $28b^+$ is not prohibitively large being between that of 1^+ and 1-adamantyl cation (Table II).

Table II. Calculated Cation Strain Energies[a]

Cation	Strain, kcal/mol	Δ strain (cation − hydrocarbon),[b] kcal/mol
6^+	48.04	13.19
$28a^+$	44.23	16.23
$28b^+$	44.51	16.51
1^+	33.20	22.51
1-Adamantyl	18.46	11.59

[a] Empirical force field employed; *cf.* ref 19. [b] See Table I for calculated hydrocarbon strain energies.

The stereochemical relationship between the migrating group and empty p orbital at the adjacent carbocation center also favors our proposed mechanistic pathway. Dihedral angles near 0° are present for each step in the proposed route, whereas alternative migrations often involve unfavorable stereochemical relationships with dihedral angles closer to 90°. Approximate dihedral angles for the various bond migrations from **6**, as measured from framework models, are given in Chart IV.

The proposed mechanism including cationic intermediates on the pathway from **6** is summarized in Chart V. As rearrangement of **2**/**3** to **6** by any pathway in Chart I would involve energetically accessible secondary norbornyl-type cations, the mechanism predicted from hydrocarbon energies should prevail. 6^+ (Chart IV) is the most likely tertiary cation to form by hydride abstraction from **6**; the alternatives are strained bridgehead norbornyl carbocations.[5] Rearrangement of 6^+ should favor formation of 24^+ over 23^+, since the latter is derived from the more strained hy-

Chart IV. Possible Cationic Intermediates from 6

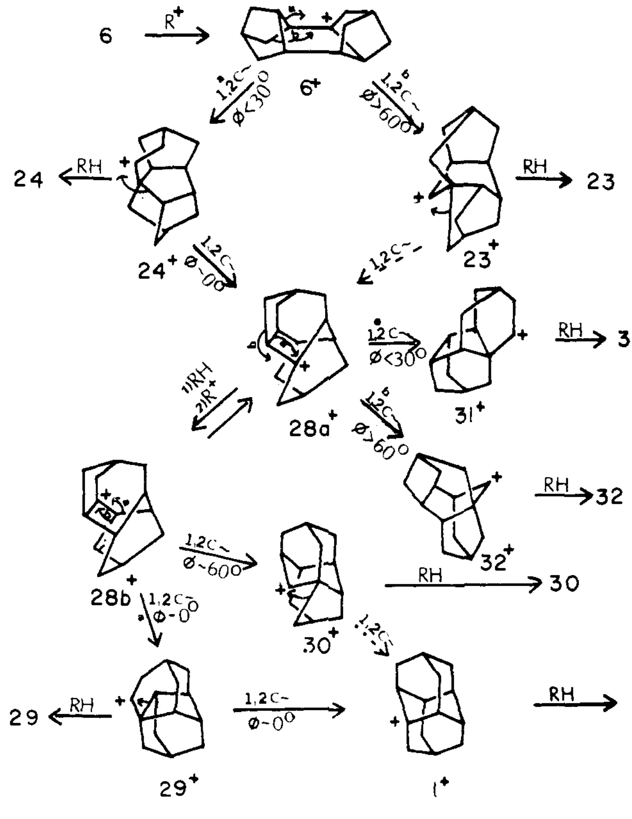


Chart V. Proposed Mechanism

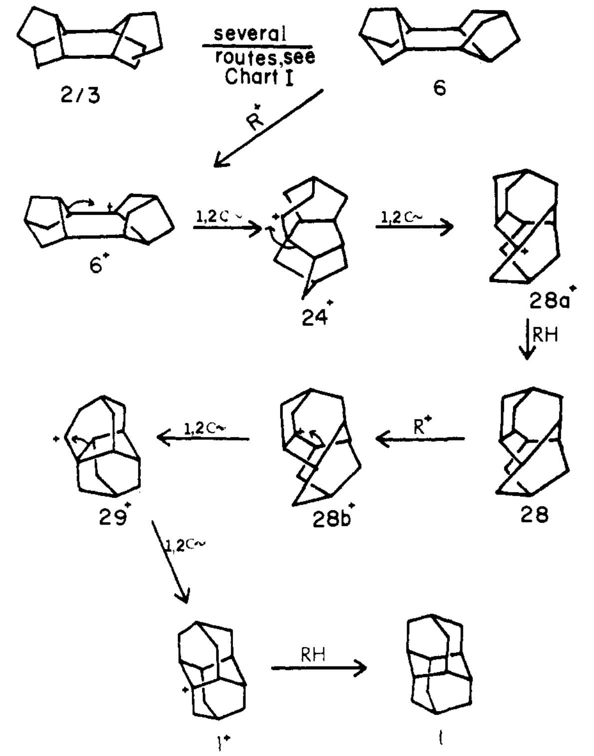
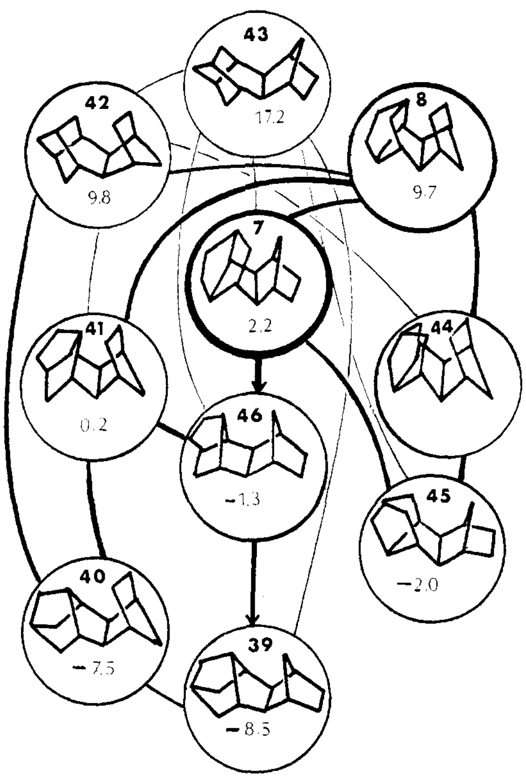


Chart VI. [2 + 4] Hydrogenated Katz Dimer Graph[a]



[a] For method of graph construction and elucidation, see Chart I, footnote *a*.

drocarbon, **23**. However, both of these secondary ions can give the same tertiary cation $\mathbf{28a}^+$. Transformation of $\mathbf{28a}^+$ to the slightly less stable $\mathbf{28b}^+$ (endothermic by 0.3 kcal/mol) is expected to take place preferentially to formation of $\mathbf{31}^+$ or $\mathbf{32}^+$, both of which are derived from higher energy hydrocarbons. Formation of $\mathbf{32}^+$ is further hindered by the unfavorable stereochemical relationship of the migrating group (dihedral angle >60°). Finally, rearrangement $\mathbf{28b}^+ \rightarrow \mathbf{29}^+ \rightarrow \mathbf{1}^+ \rightarrow \mathbf{1}$ is more favorable than $\mathbf{28b}^+ \rightarrow \mathbf{30}^+ \rightarrow \mathbf{1}^+ \rightarrow \mathbf{1}$, since $\mathbf{30}^+$ is derived from the highly strained protodiamantane **30**.

Cations $\mathbf{6}^+$ and $\mathbf{24}^+$ should be the highest energy intermediates involved (Table II, Chart IV). The remaining steps after $\mathbf{24}^+$ leading to **1** should be facile except for $\mathbf{28b}^+ \rightarrow \mathbf{29}^+$ which is expected to be endothermic; not only is $\mathbf{29}^+$ secondary but **29** is also of higher energy than **28**. However, hydrocarbons farther along the rearrangement pathway than **6** were not observed experimentally. If formation of $\mathbf{24}^+$ is taken as rate determining, then the isomerization of $\mathbf{28b}^+ \rightarrow \mathbf{29}^+$ may be endothermic without buildup of **28**.

Generalized Pentacyclotetradecane Rearrangement Graph. If the mechanism proposed for conversion of **2/3** to **1** proceeds *via* at least two tetrasubstituted intermediates, then by excluding tetrasubstituted isomers both **28** and **1** should form closed sets of interconvertible structures. Employing the SECS[10-17] computer program and investigrating every possibility by 1,2 shifts except for tetrasubstituted isomers, a set of 293 isomers (family-[1,2,4] [3,5,6], Figure 2) was generated from **28**. Similarly, **1** gave a closed set of 119 hydrocarbons (family-[1,3,5] [2,4,6], Figure 2). Similarly, the tetrahydro-Binor-S isomers are members of family-[1,2,3] [4,5,6]. These bracketed designations are derived from the most stable member of each set (**28**, **1** and **6**).

Other diamantane precursors, *e.g.*, **7**, **8**, **9**, **10**, and **11**, are not present in the above families. Experimentally, these precursors gave lower yields of **1**.[6] Applying the same assumptions as for **2/3**, **28**, and **1**, precursor **7** generated a closed family related to the [2 + 4] hydrogenated Katz dimers shown in Chart VI. Precursor **11** gave the [2 + 2] norbornene dimer-related family in Chart VII. The least strained isomer **9** gave higher yields of **1** than other [2 + 2] norbornene dimers. The families generated from the various precursors are all separated and interconverted by tetrasubstituted hydrocarbons. The experimental isolation of **6** and **39** during rearrangement of **2/3** and **7/8**, furthermore, leads to the prediction that conversion of isomers from one family to another involves initial isomerization within the family to the lowest energy product, in this case **6**, and **39**, from which the tetrasubstituted molecule is formed which provides entry into the next family of isomers. Calculations indicate that formation of the tetrasubstituted intermediates are usually higher energy processes than those involving isomerization within families. Furthermore, it appears that tetrasubstituted intermediates formed from more strained members of a family are more strained than tetrasubstituted isomers formed from the less strained members of the family.

The generalized mechanism is summarized in Chart VIII. Presumably highest yields of diamantane should be obtained from precursors belonging to families "closest" to diamantane. If isomer **28** is the lowest energy structure of family [1,2,4] [3,5,6] then experimental detection of **28** may be possible by starting with another member of family [1,2,4] [3,5,6] and carrying out an isomerization under very mild conditions.

Computer Programs

The simulation and evaluation of chemical synthesis (SECS) program[10] was originally written to design and evaluate organic syntheses, but the generality of the program enables its use in solving problems of very different types.[11] The program is written in Fortran IV for a Digital Equipment Corporation PDP-10 computer with an Evans and Sutherland display (LDS-1) system. In practice, the

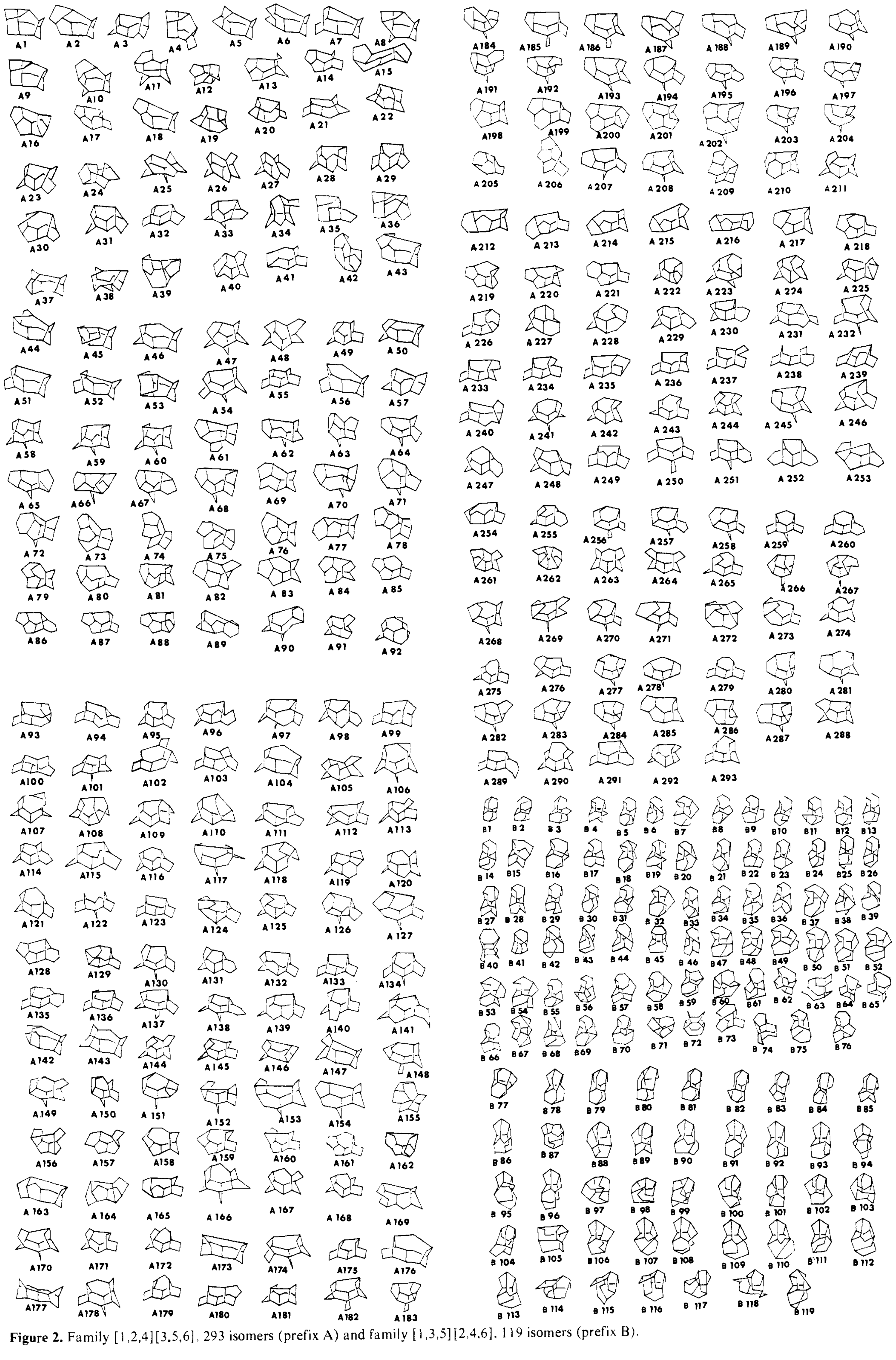
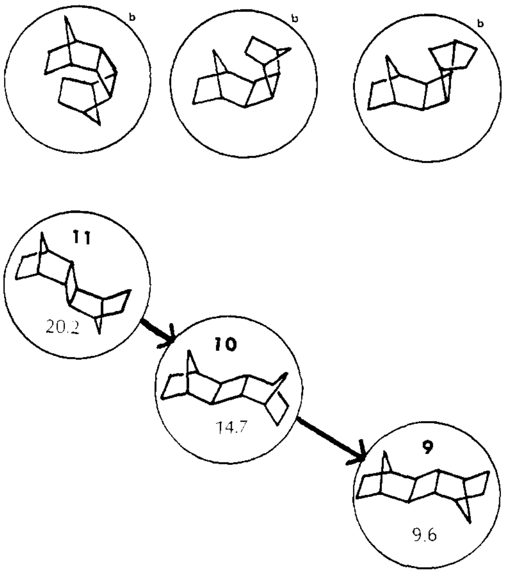


Figure 2. Family [1,2,4][3,5,6], 293 isomers (prefix A) and family [1,3,5][2,4,6], 119 isomers (prefix B).

```
TYPE PATTERN
;1,2-MIGRATION             H-C1-C2-C3  =>  C3-C1-C2-H
MIG-1-2
CH-C-C/
PRIORITY 50
        IF ATOM ALPHA TO ATOM 1 OFFPATH IS WITHIN BETA
        & TO ATOM 3 OFFPATH THEN KILL
        IF ATOM 2 IS SECONDARY THEN KILL
        IF ATOM 1 IS TERTIARY THEN KILL
        BREAK BOND 2
        MAKE BOND FROM ATOM 1 TO ATOM 3
        LOSE STEREOCHEMISTRY AT ATOM 1
        LOSE STEREOCHEMISTRY AT ATOM 2
        END
COMPLETE
```

Figure 3. ALCHEM statements necessary for generating the [1,3,5][2,4,6] and [1,2,4][3,5,6] families.

Chart VII. [2 + 2] Norbornene Dimers[a]



[a] For graph construction and elucidation, see Chart I, footnote *a*. [b] Unknown [2 + 2] *cis*-norbornene dimer. Placement at the top of chart indicates that these are more strained than the trans isomers; accurate values were not obtained, however.

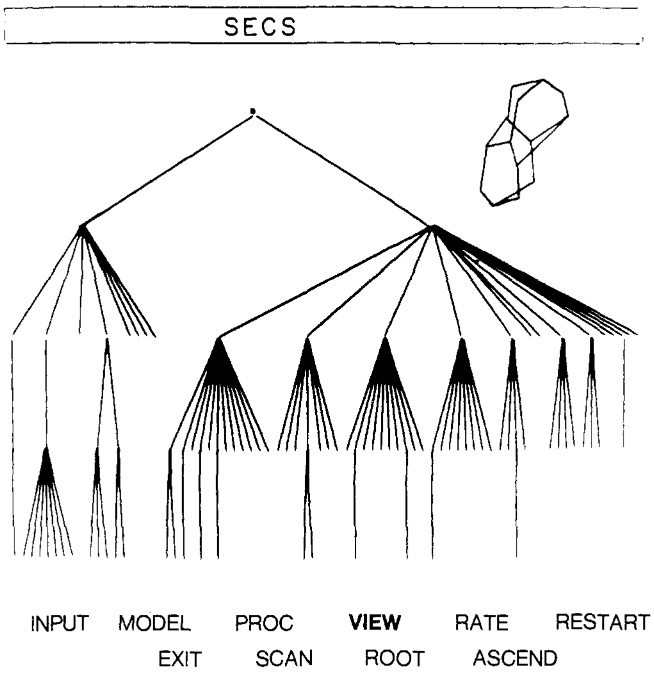
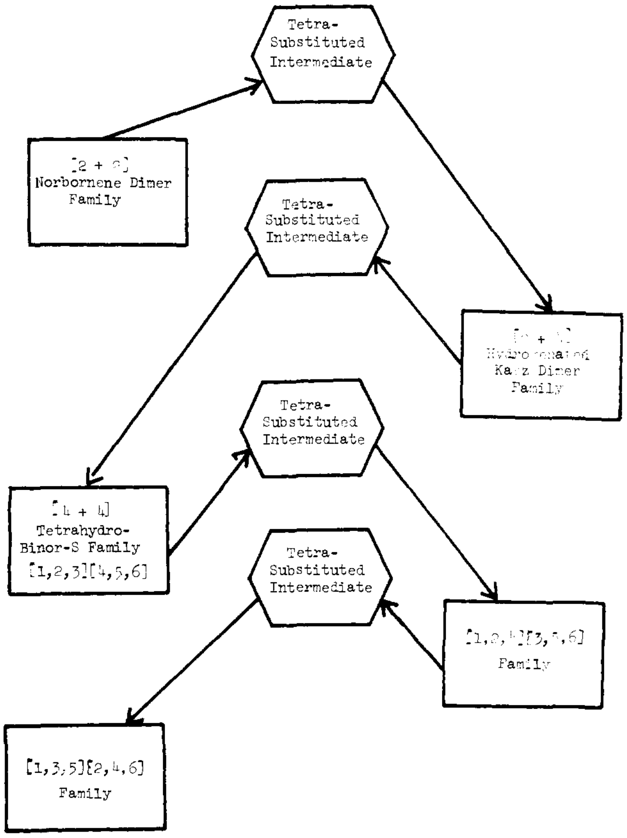


Figure 4. Partial computer generated tree of family [1,3,5][2,4,6]. The starting isomer for tree generation was diamantane. The end of each line corresponds to a structure in Figure 2B.

Chart VIII. Generalized Diamantane Mechanism[a]



[a] Ordinate is an approximate energy scale. Tetrasubstituted intermediates in each case are higher in energy than the families preceding them. Each family of isomers closer to diamantane decreases in energy.

chemist enters a molecule for analysis by drawing a standard structural diagram in the usual manner with a spark pen and acoustic tablet.[12] The stereochemistry at each ring juncture must be designated and we made the simplifying assumption that only the more stable stereoisomers need be considered in such thermodynamically controlled processes.

After completing entry of the target molecule, the chemist designates that input is "DONE" and then enters "MODEL" mode. The SYMIN (synthesis minimization) module[14] then builds a three-dimensional model from the two-dimensional structural diagram by minimizing strain due to bond lengths, bond angles, dihedral angles, nonbonded interactions, and a stereochemical strain term which assures that the proper molecular configuration is maintained. The program does not treat hydrogen atoms explicitly, but compensated in the nonbonded term by using a larger van der Waals radius for the carbon atoms. This model building provides good molecular geometries but only approximate strain energies.

The chemist then activates the PROCESS mode and SECS begins processing the selected structure. First it recognizes all rings,[15] and common functional groups, and assigns the structure a unique name,[16] which is later used by the program in eliminating duplicate structures. Next, SECS automatically begins generation of the first level of the synthesis tree using a library of synthetic transforms; in this instance, the only transform employed was 1,2-alkyl migration. The basic transform is written in ALCHEM (associative language for chemistry),[17] an English-like language understandable by both man and machine. The ALCHEM statements necessary for generating the diamantane and bicyclooctane related trees are given in Figure 3.

For every occurrence in the target structure of the pattern H-C-C-C, the statements of the transform are evaluated. For this problem the priority feature[7,10] was not used.

The first three statements prevent formation of three- and four-membered rings, primary and quaternary carbon atoms, respectively. The next two statements break and make the bonds required for the migration and the last statements indicate that stereochemistry is to be ignored. The program generates all precursors derivable from the target structure by this 1,2-alkyl migration which satisfy the criteria of the ALCHEM statements; the precursors are evaluated and duplicates are deleted. The chemist then selects one of the new structures for processing and continues in this manner until the desired final structure is obtained or until new structures are no longer generated. Figure 4 represents the partial isomer tree of the diamantane-related family. By varying the statements in Figure 3, SECS generates isomers with new assumptions, *e.g.*, deleting "IF ATOM 1 IS TERTIARY THEN KILL" allows generation of isomers containing tetrasubstituted atoms.

Other types of rearrangement mechanisms can also be represented and, in fact, multiple mechanisms can be utilized in generation of a particular isomer graph.

Conclusion

A general method has been devised for the deduction of carbocation isomerization pathways in systems too complex for complete graphical analysis.[2b] From a given starting material, the most stable isomer derived by 1,2-shifts is determined by empirical force field calculations. It is necessary to make sure that these 1,2-shifts involve carbocations of reasonable energies and which have appropriate orbital dihedral angles with regard to the migrating group. Each new isomer is processed similarly until the lowest energy rearrangement product is revealed. The lowest energy pathways derived provide a framework for experimental investigation, *e.g.*, isolation of intermediates, labeling studies, etc.

Acknowledgment. This research was supported by National Institutes of Health Grants GM-19134 and RR-00578 from the Division of Research Resources and was conducted in the Princeton Computer Graphics Laboratory. Additional support was provided by the National Science Foundation and Hoffmann-La Roche, Nutley, N.J. Computer time was provided by Princeton University. We wish to thank Drs. Clark W. Still, Thomas Dyott, and Thomas Brownscombe and Mr. Peter Friedland for their contributions to the development of the SECS computer program used in this study.

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