Application of Force Field Calculations to Organic Chemistry. Part 7.[1] Steric Interpretation of Thermolysis, Homoketonization, Ring Enlargement, and Acid-catalysed Rearrangement of Strained Cage Molecules

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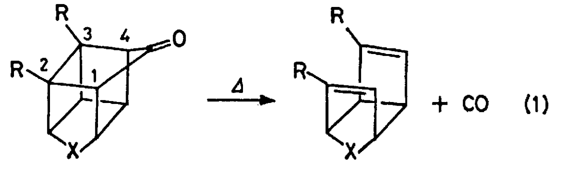
Empirical force field calculations are applied to elucidate various types of reaction mechanisms for strained cage molecules. Rates of novel thermal decarbonylation in homologous series of homocubanone derivatives (1; R = phenyl) increase with the calculated strain of the C(2)–C(3) bond, which in turn is strongly influenced by the length of alkylene bridge X, two bonds away from the C(2)–C(3) bond. The remarkable sensitivity of the rates on the calculated C(2)–C(3) bond strain is interpreted in terms of a reactant-like transition state. In contrast, thermolyses, homoketonizations, cationic ring enlargements, and anionic rearrangements of birdcage and homocubyl systems are shown to proceed through product-like transition states based on highly selective formation of the thermodynamically most stable product. The most favourable pathway is presented for a novel acid-catalysed multi-step rearrangement of a bisethanocubanedione derivative (29) to a bisnordiamantanedione derivative (30) based on enthalpy calculations of the intermediate carbonium ions. The failure to produce the ' stabilomer ' upon acid treatment of (29) under ordinary conditions is attributed to the absence of a mechanistically acceptable path for further skeletal isomerization.

In experimental organic chemistry, a number of cases are known where the results appear to be interpretable in terms of steric effects and yet no convincing explanation can be given only because precise information on the steric energy and structure of the molecule in question is lacking. This problem can be largely overcome by the use of empirical force field (molecular mechanics) calculations.[2,3] In this paper, we analyse several ring opening and rearrangement reactions of strained cage molecules which have previously been open only to vague interpretation. As they are free of conformational mobility, cage molecules are especially favourable for such analysis.

Thermolysis of Cage Ketones.—Recently, Mukai and his co-workers[4] found a novel decarbonylation of a series of cage ketones (1; R = phenyl), wherein the reactivity of (1) is greatly influenced by the size of group X, two bonds away from the sites of reaction. The rate increases in the order X = CH_2 (no reaction), CH_2CH_2, none (no bond exists), $CH_2CH_2CH_2$, and $CH{=}CHCH_2$ (Table 1, second line from the top). Based on an inspection of molecular models, Makai *et al.* reasoned that the C(2)–C(3)-bond of (1) is more and more strained as X changes in the order given above and the increased strain in this bond leads to the higher reaction rate. In view of the well recognized tendency of conventional molecular models to overemphasize angle strain while neglecting other strain sources such as stretch and torsion, it appeared worthwhile to subject this system to more sophisticated treatment, that of the Allinger force field calculations.[5,†]



(1) (2)

TABLE 1

Dependence on X of observed relative rates of decarbonylation reaction (1), calculated strain in bond C(2)–C(3), and calculated heat of reaction (1) for polycyclic cage ketone (1) according to the Allinger 1971—1972 force field[a] (kcal mol^{-1}; 25°)

		X				
		CH_2	CH_2CH_2	None	$CH_2CH_2CH_2$[b]	$CH{=}CHCH_2$[b]
Relative rate of reaction (1)[c]		0	1	95.6	214	
Strain in bond C(2)–C(3)	Stretch	0.38	0.41	0.42	0.49	0.54
	Bend	11.42	12.45	12.87	13.04	13.11
	Stretch-bend	−1.12	−0.92	−0.97	−1.03	−1.07
	Torsion	1.81	1.07	1.52	1.49	1.51
	Nonbonded	−0.47	−0.40	−0.38	−0.37	−0.35
	Sum	12.02	12.61	13.46	13.62	13.74
	Strain energy[d]	16.38	16.97	17.82	17.98	18.10
Heat of reaction (1), $\Delta H°_R$[e]		−213.02	−219.38	−219.30	−226.63	−223.70

[a] Ref. 5. [b] X in *anti*-conformation with regard to carbonyl group. [c] Ref. 4. [d] For definition see text and footnote * on p. 182. [e] $\Delta H_f°(2) + \Delta H_f°(C{=}O) - \Delta H_f°(1)$. $\Delta H_f°(2)$ values not listed in Table 1 taken from E. Ōsawa, K. Aigami, and Y. Inamoto, *J. Org. Chem.*, 1977, **42**, 2621. $\Delta H_f°(C{=}O)$ −257.3 kcal mol^{-1}, taken from G. Glocker, *J. Phys. Chem.*, 1958, **62**, 1049.

For technical reasons, calculations were performed only on (1; R = H) and (2; R = H) (Table 2)

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† The Allinger 1971—1972 force field was thereafter updated twice.[6,7] However, the original force field was used throughout this work unless otherwise noted.

TABLE 2

Calculated heats of formation and strain energies of polycyclic cage ketones and diolefins derived therefrom upon decarbonylation according to the Allinger 1971—1972 force field [a] (kcal mol^{-1}; 25°; gas phase)

		ΔH_f°	Strain energy
Pentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decan-6-one (1,3-bishomocubanone) (1; X = CH_2, R = H)		32.14	86.73
Pentacyclo[5.4.0.0^{2,5}.0^{3,9}.0^{4,8}]undecan-6-one (1; X = CH_2CH_2, R = H)		23.73	83.51
Tetracyclo[4.3.0.0^{2,5}.0^{3,8}]nonan-9-one (dihydrohomocubanone) (1; X = none, R = H)		25.62	81.09
Pentacyclo[5.5.0.0^{2,5}.0^{3,9}.0^{4,8}]dodecan-6-one (1; X = $CH_2CH_2CH_2$, R = H)	*anti* [b]	23.85	88.82
	syn [b]	24.80	89.77
Pentacyclo[5.5.0.0^{2,5}.0^{3,9}.0^{4,8}]dodec-10-en-6-one (1; X = $CH{=}CHCH_2$, R = H)	*anti* [b]	53.37	91.01
	syn [b]	53.69	91.33
Tricyclo[4.3.2.0^{2,5}]undeca-3,7,10-triene (2; X = $CH{=}CHCH_2$, R = H)	*anti*,[c] twist	86.97	49.93
	anti,[c] eclipse	86.91	49.87
	syn,[c] twist	86.91	49.87
	syn,[c] eclipse	86.90	49.86
syn,cis-Bicyclo[4.2.0]octa-4,7-diene (2; X = none, R = H)		63.64	44.43

[a] Ref. 5. [b] Conformation of X bridge relative to carbonyl group. [c] Conformation of $CH{=}CHCH_2$ bridge relative to C(10)–C(11) double bond.

even though they actually do not undergo the decarbonylation reaction but revert to dienone upon thermolysis.[4] Nevertheless, the trend in strain and enthalpy changes in this series should be little affected by replacing the phenyl group with hydrogen. We first checked if there really was significant dependence of strain in the C(2)–C(3) bond on the length of X. In the force field method, however, all the forces acting within a molecule are originally partitioned not between bonds but among atoms. In order to evaluate strain in the bond, we must first sum up all the steric factors acting across this bond. For this purpose, the following components are considered: (1) the stretch energy of the bond C(2)–C(3); (2) the sum of bending and stretch-bend energy terms involving the C(2) and C(3) atoms as in C(1)$\widehat{\mathrm{C}}$(2)C(3); (3) the sum of torsional energies involving, the C(2)–C(3) bond as in the central unit C(1)–C(2)–C(3)–C(4); (4) the sum of non-bonded 1,4-interactions across the C(2)–C(3) bond such as C(1) · · · C(4).

The total of these four terms, ΔH^b, should give a measure of localization of steric energy *on* the bond C(2)–C(3). If one extends Allinger's definition of molecular strain [5a] to the bond, the 'bond strain' for a C_{tert}–C_{tert} bond such as C(2)–C(3) can be formulated [*] as bond strain energy = $\Delta H^b + 4.36$ kcal mol^{-1}.

Results of analysis (Table 1) reveal that the C(2)–C(3) bond strain does indeed increase with increasing decarbonylation rate. However, besides the problem of the significance and error range of these strain figures which are hard to determine in the absence of experimental standards for the bond strain values,[†] the changes in calculated bond strain with X are much smaller than expected from the observed dependence [4] of the reactivity of (1) on X. We tentatively give the following explanation for this difficulty. Our force field calculations allow accurate estimates of the heats of reaction.[1,3a,8] As shown in the last line (ΔH_R^0) of Table 1, this reaction is strongly exothermic, mainly because of the large heat of formation of carbon monoxide. Hence, it is likely that the transition state is close to reactant (1) and thus is sensitive to small differences in the strain of the C(2)–C(3) bond.[‡]

On the other hand, the possibility of reaction (1) having a diolefin-like transition state is highly unlikely. This would require an energy 200 kcal mol^{-1} larger than the anticipated exothermicity and the order of observed rates does not agree with that of the heat of reaction, ΔH_R^0, which governs the relative rates of reactions having product-like transition states.[8]

Thus, reaction (1) seems to present a unique example of local bond strain of 'mechanical origin' strongly affecting the reaction of strained cage molecules. Contrasting cases wherein the total balance of molecular strain determines the course of reaction are found more often in the chemistry of cage molecules, and these reactions are mentioned in the next section.

Thermodynamic-controlled Ring Opening of Cage Molecules.—Several remarkably selective ring opening reactions have been known for some cage molecules with birdcage and homocubane skeletons. Table 3 summarizes reported results of thermolysis, base-catalysed homoketonization, and cationic ring expansion reactions. Despite the multiple possibilities for the direction of ring opening (α, β, and γ), a single product always results. The observed high specificity has been vaguely

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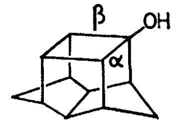
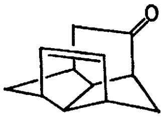
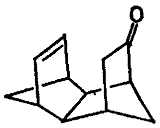
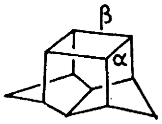
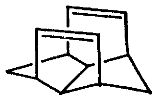
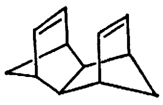
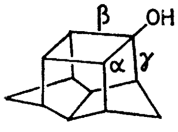
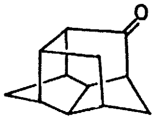
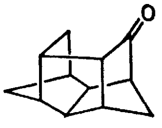
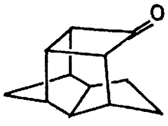
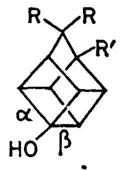
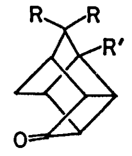
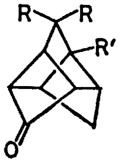
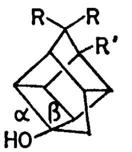
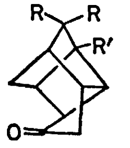
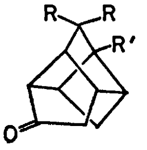
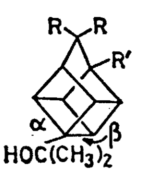
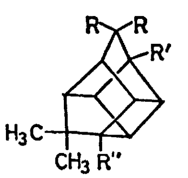
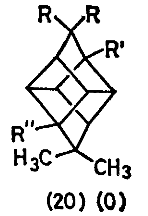
[*] In analogy to Allinger's definition of molecular strain,[5a] 'bond strain' can be formulated as: bond strain = $\Delta H_f^b - \Delta H_f^{b,s}$ with $\Delta H_f^b = \Delta H^b + C$ where ΔH_f^b is the hypothetical 'heat of bond formation,' $\Delta H_f^{b,s}$ the 'strainless heat of bond formation,' ΔH^b the 'bond steric energy' (see text), and C the sum of correction terms which depend on the type of atoms comprising the bond in question. According to Allinger,[5a] $C = 1.49$ and $\Delta H_f^{b,s} = -2.87$ kcal mol^{-1} for bonds of the C_{tert}–C_{tert} type. Substitution of these constants into the first equation gives the equation described in the text.

[†] Although the changes in calculated bond strain among homologous series of (1) are smaller than the accuracy range for the calculations (± 1.2 kcal mol^{-1}) [1,5] of this force field, we think they are still of some significance. First, the calculated strain concerns itself with a small fragment of the molecule and the error range should be smaller than that for molecular strain. Secondly, when relative energies among structurally closely related isomers are compared, the accuracy of energy calculations must be greatly improved because errors inherent to the force field should cancel each other.

[‡] The coincidence of our computational conclusion with that based on molecular models apparently arises from the fact that C(2)–C(3) bond strain is dominated by the angle strain term (Table 1), which can fortunately be detected by molecule models albeit to somewhat exaggerated extent.

TABLE 3

Calculated enthalpies and strain energies (kcal mol^{-1}) of possible products from thermolysis, homoketonization, and ring expansion of cage molecules according to the Allinger 1971—1972 force field [a]

Substrate	Product[b] (% yield) α	β	γ	Ref.	$\Delta H_f°$	Strain energy	$\Delta H_R°$ [c]
Thermolysis							
 (3)	 (4) (95)[d]	 (5) (0)		9*b*	(4) −15.46 (5) 4.92	28.25 48.63	
 (6)	 (7) (75)	 (8) (0)		9*b*	(7) 35.65 (8) 59.74[f]	25.06 49.15[f]	4.01[e]
Homoketonization							
 (3)[g]	 (9) (96)	 (10) (4)	 (11) (0)	9, 10	(9) −27.38 (10) −14.10 (11) −0.39	37.59 50.87 64.58	
 (12)[i]	 (13) (100)	 (14) (0)		11, 12	(13)[h] 25.93 (14)[h] 35.13	81.40 90.60	
 (15)[i]	 (16) (100)	 (17) (0)		11	(16)[h] −9.20 (17)[h] −5.05	51.46 55.61	
Ring expansion with HBr							
 (18)	 (19) (100)	 (20) (0)		13	(19)[h] 37.63 (20)[h] 39.35	80.31 82.03	5.82[j]

R, R = O(CH$_2$)$_2$O, R′ = R″ = Br

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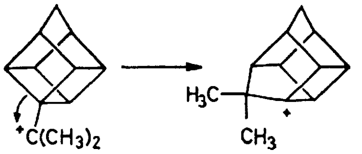
[a] Ref. 5. [b] IUPAC names: (4), all-*cis*-tetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodec-2-en-7-one; (5), tetracyclo[6.2.1.1^{3,6}.0^{2,7}]dodec-4-en-9-one; (7) all-*cis*-tetracyclo[7.2.1.0^{4,11}.0^{6,10}]dodeca-2,7-diene; (9), pentacyclo[7.2.1.0^{2,8}.0^{4,11}.0^{6,10}]dodecan-3-one; (10), pentacyclo[7.2.1.0^{2,6}.0^{3,10}.0^{4,8}]dodecan-7-one; (11), pentacyclo[5.4.1.0^{2,6}.0^{3,10}.0^{8,11}]dodecan-9-one; (13), 1-bromo-9,9-ethylenedioxytetracyclo[4.3.0.0^{2,5}.0^{3,8}]nonan-4-one; (14), 7-bromo-8,8-ethylenedioxytetracyclo[4.3.0.0^{3,9}.0^{4,7}]nonan-2-one; (16), 1-bromo-10,10-ethylenedioxytetracyclo[5.3.0.0^{2,6}.0^{3,9}]decan-5-one; (17), 5-bromo-6,6-ethylenedioxytetracyclo[5.3.0.0^{2,5}.0^{4,8}]decan-9-one; (19), 5,9-dibromo-6,6-dimethyl-10,10-ethylenedioxypentacyclo[5.3.0.0^{2,5}.0^{3,9}.0^{4,8}]decane; (20), 6,9-dibromo-5,5-dimethyl-10,10-ethylenedioxypentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane. [c] Calculated heat of reaction. See footnote * on p. 184 for more calculations based on the MMI force field. [d] Trace amount of (9) was formed, 9*b*. [e] Calculated enthalpy of (6) taken from ref. 14. [f] Taken from E. Ōsawa, K. Aigami, and Y. Inamoto, *J. Org. Chem.*, 1977, **42**, 2621. [g] Base is t-butoxide. [h] Calculated energy values refer to model compounds where R, R′, and R″ are replaced with H. [i] Base is methoxide. [j] Based on carbonium ion models and Engler force field.[14] Heat of formation relative to t-butyl carbonium ion with corrections for α- and β-branching.[15] Calculated $\Delta\Delta H_f$ of $(18)^+$ ($R = R' = H$, OH replaced by +) is 102.11 and that of $(19)^+$ 107.93 kcal mol^{-1}.

suggested to arise from smaller steric strain in the isolated product resulting from the opening of bond α compared with those from the opening of bond β (or γ).

The results of our force field calculations are in accord with these earlier suggestions. Columns 6 and 7 of Table 3 list enthalpies and strain energies of possible products resulting from the opening of the α, β, and γ bonds. Thermolyses of birdcage alcohol (3) and its parent hydrocarbon (6) lead to the thermally more stable products, (4) and (7), respectively.[9] Strain analysis indicates that higher steric energy of (5) [and (8)] relative to (4) [and (7)] arises from the large angle strain present at the central three-carbon unit of the two norbornane partial structures.

The reversible, base-catalysed homoketonization of birdcage alcohol (3), and homo- (12) and bishomocubanol (15) should produce the most stable isomer among the possible products under the equilibrium conditions. Selective formation of virtually one product in each instance reported [9-12] is rationalized by the large difference in calculated enthalpies between the most stable and the next most stable product (2—13 kcal mol^{-1}, Table 3).

The regiospecificity mentioned above would have occurred if the α bond was significantly more strained than the β and γ bonds already in the ground state and reacted preferentially. Table 4 compares strain energies of the α and β bonds, as defined in the preceding section, of parent hydrocarbons (6), homocubane (21), and 1,3-bishomocubane (22). While the α bond appears more strained than the β bond in (6) and (21), the reverse is true in (22). Thus, the bond strain interpretation seems inconsistent. Nevertheless, the calculated small bond strain difference in (6) and (21) may not be overlooked if the corresponding reactions quoted in Table 3 were as strongly exothermic as reaction (1). The Allinger 1971—1972 force field allows the prediction of heat of reaction only for one example, (6) → (7), which turned out slightly endothermic (Table 3, last column). Similarly, the model ring expansion reaction, $(18)^+ \rightarrow (19)^+$ [equation (2)] is estimated to be slightly endothermic (Table 3). Thus, the product-determining steps of the reactions listed in Table 3 do not appear to be greatly influenced by those small, ground-state bond strain differences.*



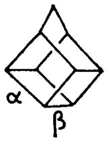
(2)

(18)$^+$ (19)$^+$

TABLE 4

Strain in two cyclobutane bonds (α and β) of birdcage hydrocarbon (6), homocubane (21), and 1,3-bishomocubane (22) and total energies of respective dihydro derivatives according to the Allinger 1971—1972 force field [a] (kcal mol^{-1})

(6)



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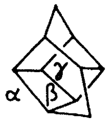
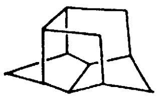


(22)

	(6) α	(6) β	(21) α	(21) β	(22) α	(22) β
Bond strain energy [b]						
Stretch	0.25	0.14	0.33	0.45	0.31	0.16
Bend	10.18	9.56	19.60	18.30	10.90	11.57
Stretch-bend	−0.66	−0.56	−1.34	−1.42	−0.76	−0.62
Torsion	2.00	2.00	2.33	2.50	1.72	1.44
Nonbonded	−0.32	−0.41	−0.43	−0.32	−0.42	−0.28
Sum	11.35	10.73	20.49	19.51	11.75	12.83
Bond strain energy [b]	15.71	15.09	24.85	23.87	16.11	17.19

Dihydro derivatives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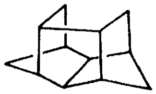
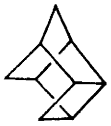

(24)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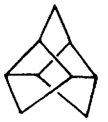
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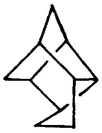
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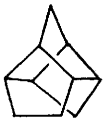
(28)

	(23)	(24)	(25)	(26)	(27)	(28)
ΔH_f°	−1.75	15.39	46.07	56.23	17.94	21.47
Strain energy	36.25	53.39	74.57	84.73	51.63	55.16

[a] Ref. 5. [b] For definition see text. [c] IUPAC names: (23), pentacyclo[7.2.1.0^{2,8}.0^{4,11}.0^{6,10}]dodecane; (24), pentacyclo[7.2.1.0^{2,6}.0^{3,10}.0^{4,8}]dodecane; (25), tetracyclo[4.3.0.0^{2,5}.0^{3,8}]nonane; (26), tetracyclo[4.3.0.0^{3,9}.0^{4,7}]nonane; (27), tetracyclo[5.3.0.0^{2,6}.0^{3,9}]-decane; (28), tetracyclo[5.3.0.0^{2,5}.0^{4,8}]decane.

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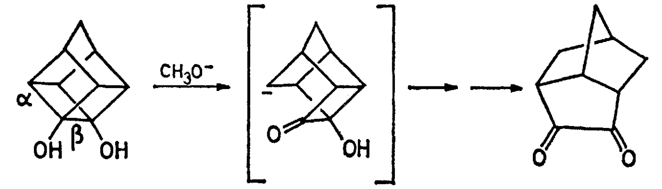
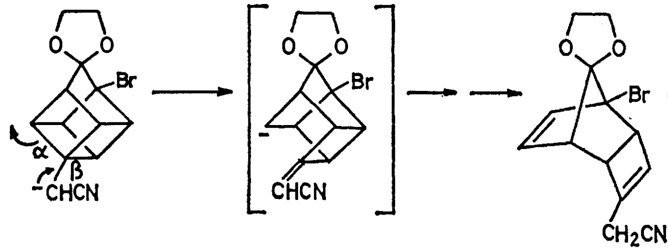
* The MMI force field [6] incorporates parameters for hydroxy and ether groups. As the present work had been completed before the MMI program became available, all compounds listed in Table 3 were recalculated with MMI. Enthalpies (kcal mol^{-1}): (3), −10.58; (4), 15.77; (6), 30.79; (7), 38.08; (9) −27.19; (12), −8.90; (13), −43.97; (15), −59.62; (16), −77.89. Heats of reaction (kcal mol^{-1}): (3)→(4), 26.35; (6)→(7), 7.29; (3)→(9), −16.61; (12)→(13), −35.07; (15)→(16), −18.27. The reactions in the Tables are either endothermic or slightly to moderately exothermic and none of them is as exothermic as reaction (1).

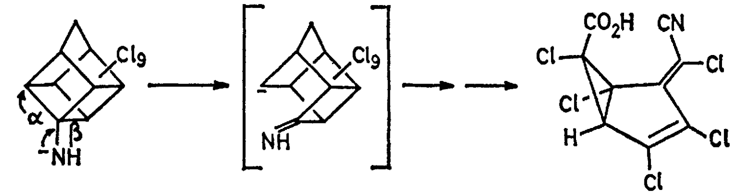
Table 4 includes calculated heats of formation for dihydro derivatives (23)—(28), derived by hypothetically hydrogenating the α or β bond of (6), (21), and (22), respectively. These dihydro molecules may be considered to provide hydrocarbon models for demonstrating product-development control of bond opening. For the three systems studied, α-dihydro derivatives are consistently more stable than the corresponding β-dihydro derivatives by margins of 4—17 kcal mol^{-1}.*



(3)[18]

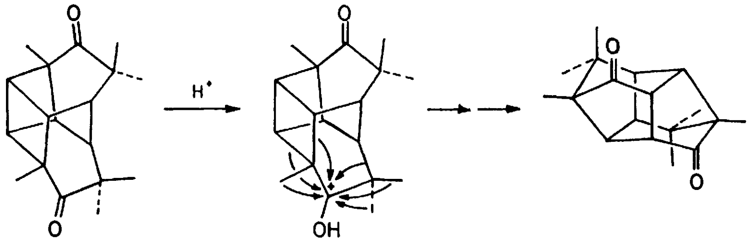


(4)[19]



(5)[20]

Several examples [equations (3)—(5)] of base-promoted, deep-seated rearrangements of homocubane derivatives have been interpreted to involve selective α bond opening as shown.



(29) (29)-H$^+$ (30) (6)

Including these carbanion rearrangements, various types of ring opening of strained cage molecules mentioned in this section can be best understood if the product-developing stage is located late along the reaction co-ordinate and thus strongly influenced by the thermodynamic stability of product.

Acid-catalysed Multi-step Rearrangement of a Cage Ketone.—Hirao *et al.*[21] recently reported a remarkably smooth transformation of a hexamethylbisethanocubane diketone (29) into a bisnordiamantane diketone derivative (30) on treatment with trifluoroacetic acid which proceeds almost instantly in quantitative yield at room temperature [equation (6)].

Such an apparently multi-step carbonium ion rearrangement as this usually leads to the most stable thermodynamic product as in 'the adamantane rearrangement.'[22] However, we know from our independent study of pentacyclododecane isomers that the parent hydrocarbon of (30) is not the most stable hydrocarbon skeleton,† and hence (30) is not likely to be the 'stabilomer'[22a] of hexamethylpentacyclododecanedione. Indeed, in the course of the preparation of re-

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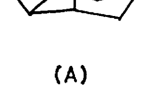
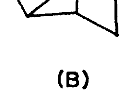
* These arguments do not necessarily lead to correct predictions of the actual hydrogenolysis products. Compound (6) has never been subjected to hydrogenolysis. Compound (21) does give (25) as the main dihydro product.[16] Catalytic hydrogenation of (22) cleaves the γ bond.[17]

† Namely, the pentacyclododecane (A) (C_{2h} point group) is 8 kcal mol^{-1} *less* stable than isomer (B) (C_2 point group, the stabilomer of the pentacyclo-C_{12} family[22a]). A similar stability relation exists for ethano- and bisethano-bridged homologues of the (A)—(B) pair.[23]


(A)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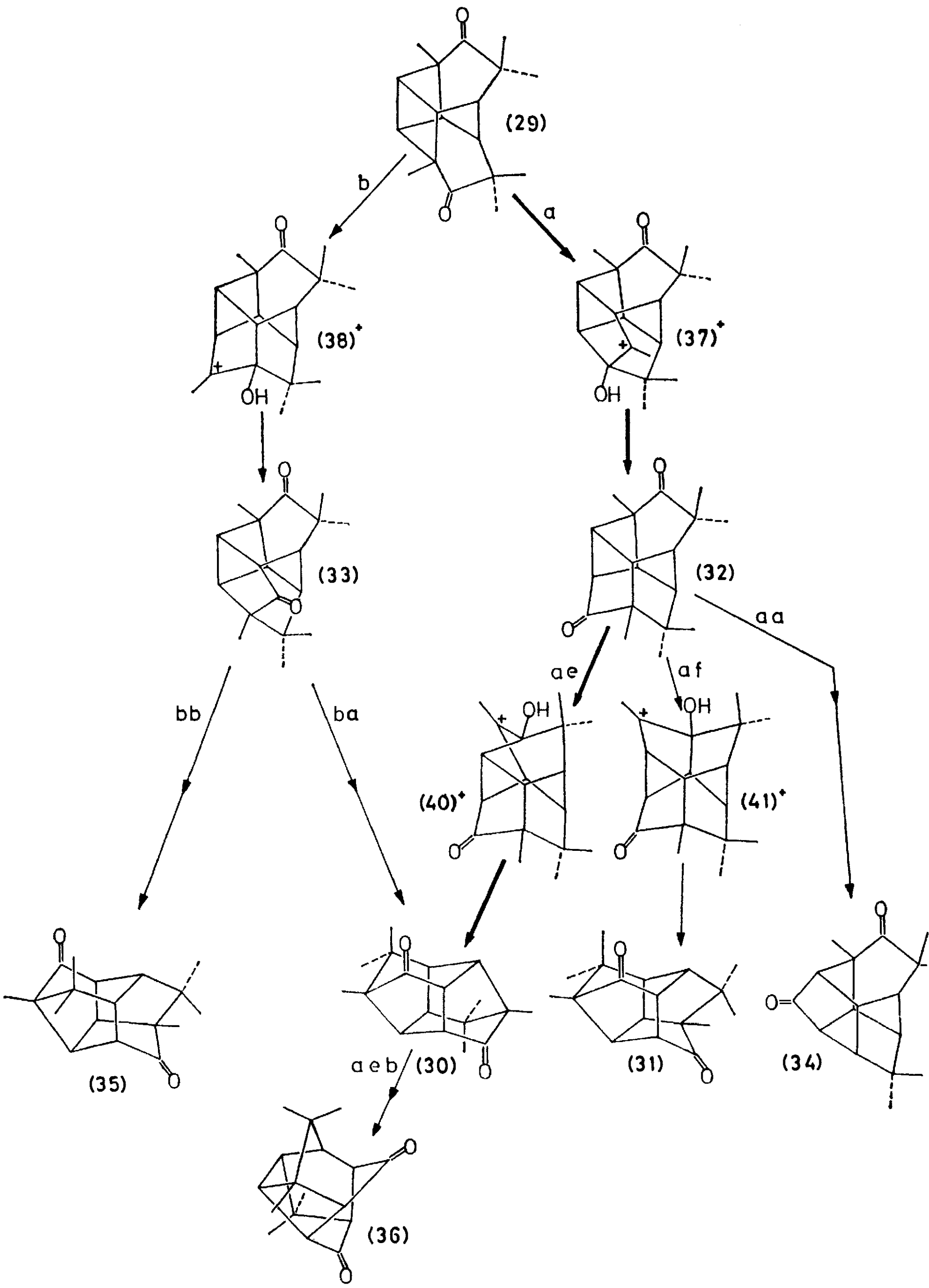

FIGURE 1 Partial map of acid-catalysed rearrangement of hexamethylpentacyclododecanediones

arrangement map (Figure 1) starting from (29) by considering every 1,2-alkyl shift possibility * and calculating enthalpies of the new isomers generated, isomers (31) and (35) are found to have calculated enthalpies 3—6 kcal mol^{-1} lower than (30) (Table 5).† It is thus of considerable interest to study the mechanistic detail of reaction (6) and to discover the reason why (30) does not rearrange further into a more stable isomer.

Compared to Lewis acid-catalysed hydrocarbon rearrangements where carbonium ions are believed to form at almost any secondary and tertiary carbon,[22] the isomerization of ketone with protic acid is simpler because the carbonyl oxygen should be exclusively protonated to generate a resonance-stabilized C^{+}–OH species (I) [equation (7)], which starts the skeletal isomerization. Furthermore, there is a feature peculiar

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* Since a large number of possible elementary rearrangement steps could exist between (29) and (30), some simplifying assumptions, justified in previous studies,[22] are also made in this work: we consider only 1,2-alkyl shifts and neglect those paths which involve a primary carbonium ion or lead to an intermediate containing exceedingly strained partial structures such as three and four-membered rings. For details of the preparation of a carbonium ion rearrangement map, see ref. 22*c*—*f*.

† Isomer (31) is probably the 'stabilomer' of hexamethylpentacyclododecanediones.

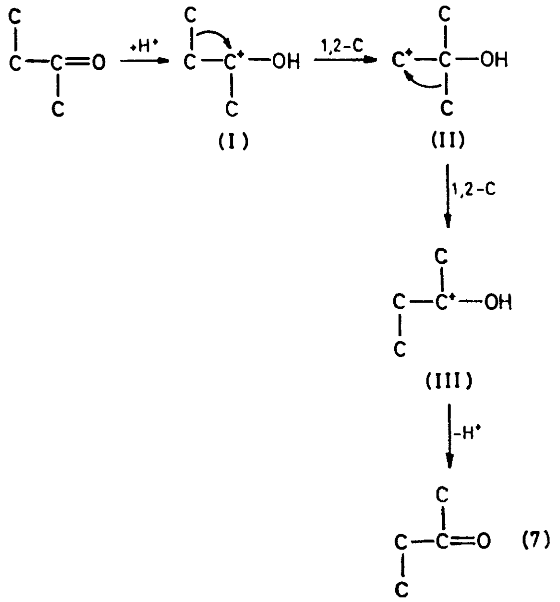
TABLE 5

Calculated heats of formation and strain energies of hexamethylpentacyclododecanediones according to the Allinger 1971—1972 force field[a] (kcal mol^{-1}: 25°)

Compound[b]	ΔH_f	Strain energy
5,7,7,10,10,12-$[6.4.0.0^{2,5}.0^{3,12}.0^{4,9}]$-6,11 (29)	−63.69	74.59
1,5,6,6,12,12-$[6.3.1.0^{2,7}.0^{3,10}.0^{5,9}]$-4,11 (30)	−87.93	50.35
5,5,6,10,10,11-$[6.4.0.0^{2,6}.0^{3,11}.0^{4,9}]$-7,12 (31)	−93.84	44.44
6,7,7,10,10,12-$[6.4.0.0^{2,6}.0^{3,10}.0^{4,9}]$-5.11 (32)	−67.46	70.82
5,7,7,11,12,12-$[6.4.0.0^{2,5}.0^{3,11}.0^{4,9}]$-6,10 (33)	−78.57	59.71
2,3,3,9,11,11-$[6.4.0.0^{2,6}.0^{4,12}.0^{5,9}]$-7,10 (34)	−84.66	53.62
6,7,7,10,10,11-$[6.4.0.0^{2,6}.0^{3,11}.0^{4,9}]$-5,12 (35)	−91.14	47.14
3,3,4,7,7,8-$[6.4.0.0^{2,6}.0^{4,11}.0^{5,10}]$-9,12 (36)	−80.85	57.43

[a] Ref. 5. [b] Abbreviated for brevity. Full IUPAC name of, for example, (29), is 5,7,7,10,10,12-hexamethylpentacyclo$[6.4.0.0^{2,5}.0^{3,12}.0^{4,9}]$dodecane-6,11-dione.

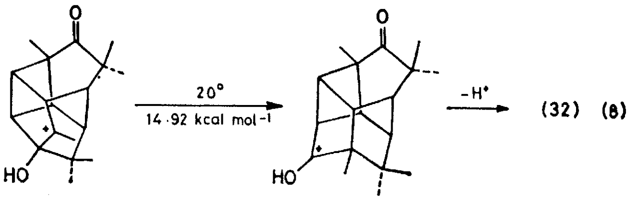
to the solvent–catalyst trifluoroacetic acid. Once a 1,2-alkyl shift occurs in (I), the new ionic centre of (II) lacks stabilization from the OH group. In the absence of hydride or other potential nucleophile, (II) is expected to rearrange into stabilized (III), if this change is more favourable than the reversion (II) ⟶ (I). Ion (III) equilibrates with a ketone isomer. The choice of the favoured path over other possibilities is made on the basis of two criteria: the calculated enthalpy of the product carbonium ion and the orbital alignment factor as defined by the dihedral angle between the vacant orbital of the ionic centre and the adjacent orbital about to migrate into the former.[22e,f,*]



(I) (II) (III) (7)

The first of consecutive steps that ensues upon treatment of (29) with trifluoroacetic acid is the formation of a protonated species (29)-H$^+$, which should formally be able to induce *six* 1,2-alkyl shifts [equation (6)]. Scheme 1 illustrates the analysis of these possibilities for hydrocarbon models, where, for example, (29)$^+$ represents (29)-H$^+$. Enthalpies of intermediate cations ($\Delta\Delta H_f$) are calculated by the Engler force field.[14,15] One of the intermediates, (37)$^+$, generated by path a, is the most stable, the advantage in energy over the next most stable intermediates, (38)$^+$ and (39)$^+$, being as large as 14 kcal mol^{-1}.† However, path a is predicted to involve an alkyl migration over a large dihedral angle (52°), whereas paths b and f involve apparently better bond alignments. Path f readily proves to be a mechanistic deadend, giving only an unstable intermediate over an unfavourable angle.‡ We follow below the consequences of paths a and b.

Path a is traced first. As mentioned above, the high energy intermediate (37)$^+$ is supposed to isomerize into an OH-stabilized carbonium ion [equation (8)]. For this isomerization, only one path is available which leads to a new diketone isomer (32) by way of (32)-H$^+$. Diketone (32) has two non-equivalent keto groups. Therefore, two hydrocarbon cation models, (32$^+$) and (32′)$^+$, need to be considered for the protonated species (Scheme 2). The calculated $\Delta\Delta H_f$ value of (32)$^+$ is *ca.* 9 kcal mol^{-1} lower than that of (32′)$^+$, and we expect



(37)$^+$ (32)-H$^+$ (32) (8)

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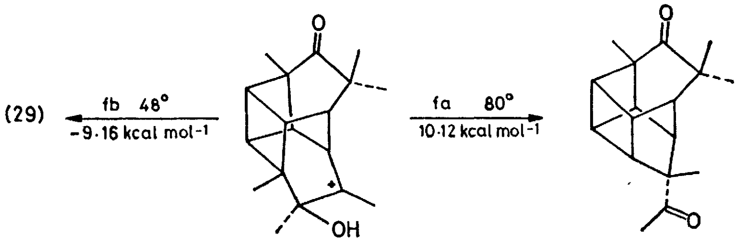
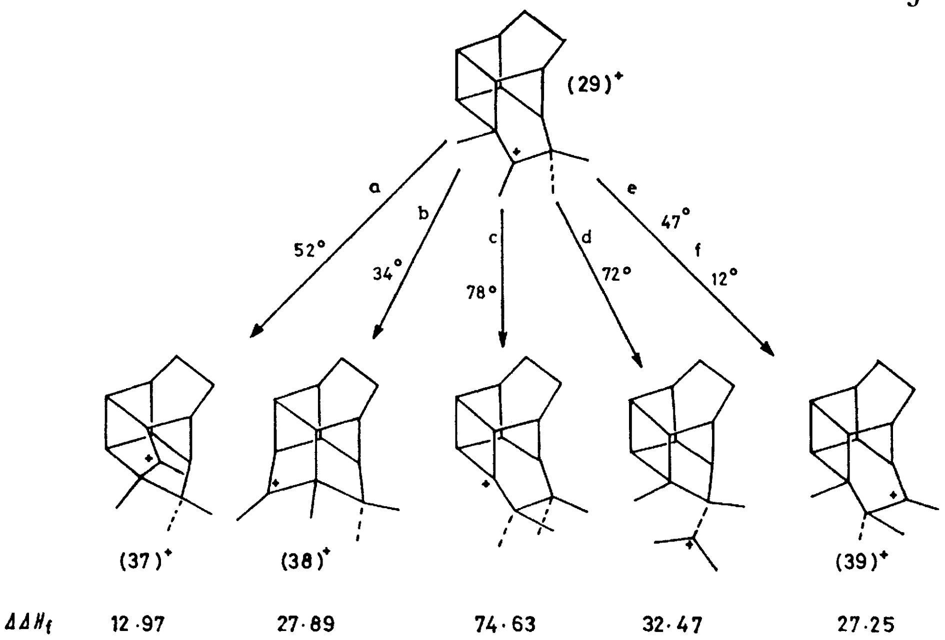
* The relative importance of the two criteria has never been studied.

† The calculated $\Delta\Delta H_f$ of (29)$^+$ is 18.09 kcal mol^{-1}. The difference of this value from $\Delta\Delta H_f$ for the products from path a—f underestimates the actual activation energy, since (29)$^+$ is a model for (29)-H$^+$ whose carbonium ion centre is stabilized (C$^+$-OH $\longleftrightarrow$ C=$\overset{+}{O}$H) while (37)$^+$ is a model for an unstabilized carbonium ion.

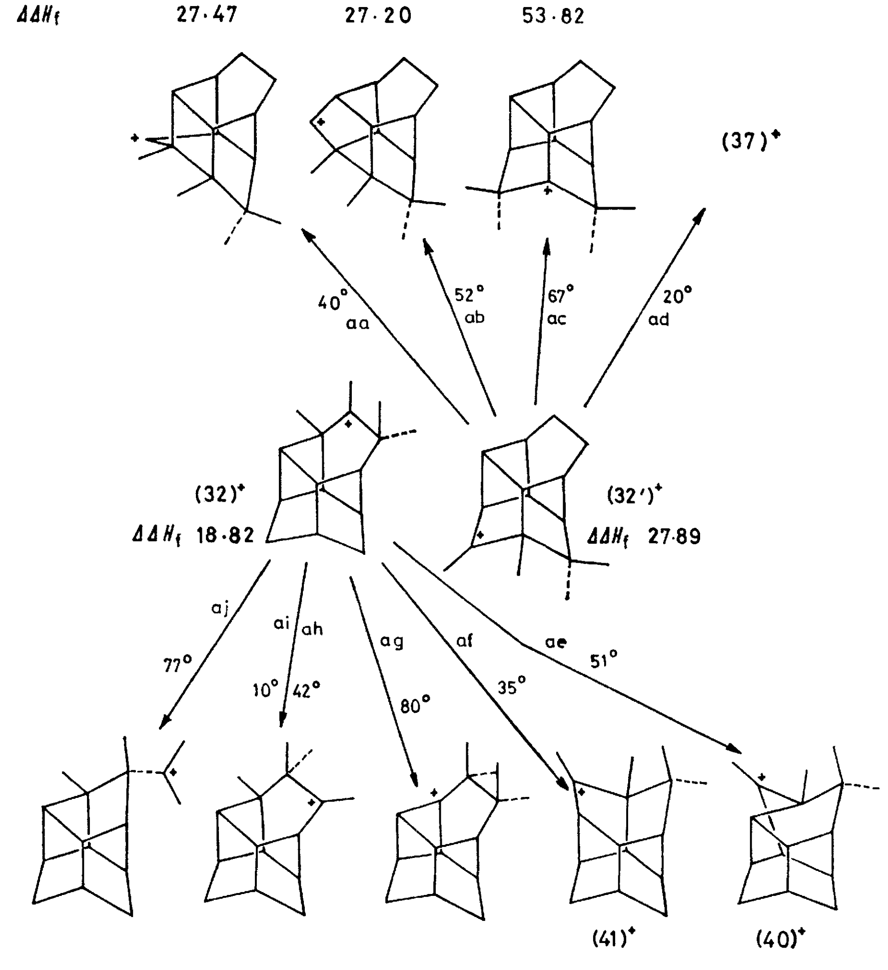
‡ Only two, further rearrangement pathways are available for (39)$^+$. Judged by our criteria, path fb is definitely more favourable than fa, but gives back the starting diketone (29).



(39)$^+$



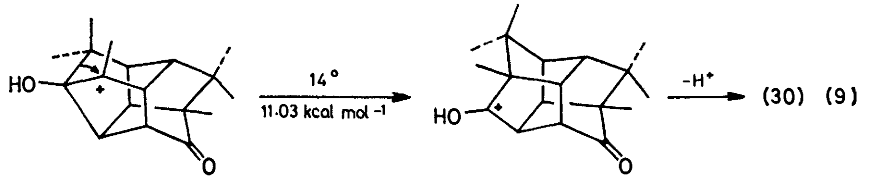
SCHEME 1



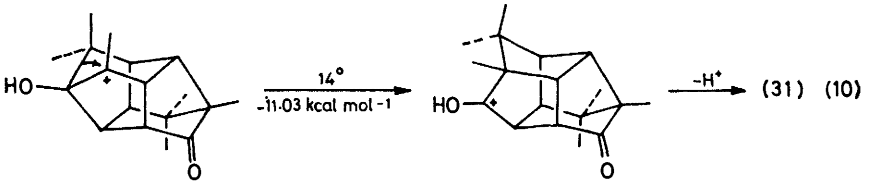
SCHEME 2

the 'upper' carbonyl group of (32) to be protonated much faster than the 'lower' carbonyl. Among the possible products resulting from a 1,2-alkyl shift in $(32)^+$, $(40)^+$ is predicted to have the lowest and $(41)^+$ the next lowest enthalpy. Actually, these two are the most stable products even including those arising from $(32')^+$. Here again, the orbital alignment in path ae appears somewhat less favourable than in path af, and it seems difficult at this point to decide which path is really favoured. In the absence of further criteria, we must follow both paths until experimental observations can be used as an additional clue.

Equations (9) and (10) illustrate the consequences of further isomerization of corresponding keto-hydroxy cations resulting from paths ae and af, respectively.



$(40)^+$ $(30)\text{-H}^+$



$(41)^+$ $(31)\text{-H}^+$

The orbital alignments in the first steps of these two reactions are equally favourable. However, judging from the $\Delta\Delta H_f$ values of hydrocarbon cation models, reaction (10) is preferred to (9). Experimentally, only (30), but no (31), was obtained.[21] This means that $(41)^+$ was never formed, and path af could not compete with the path ae (Scheme 2).

Consequently, we are led to believe that the dihedral angle difference of 15° between paths ae and af is not significant and the orbital alignment in these paths should best be regarded as ' equally unfavourable ', and that the $\Delta\Delta H_f$ values of cation products must have exerted the decisive influence on the course of reaction of $(32)^+$.

Going back to path b (Scheme 1), we can now consider this path as not significant: the orbital alignment factors for paths a and b should be considered as essentially equal and then path b does not appear to be able to compete with path a because of the large difference in $\Delta\Delta H_f$ between $(37)^+$ and $(38)^+$.*

Thus, according to our analysis, the most favourable

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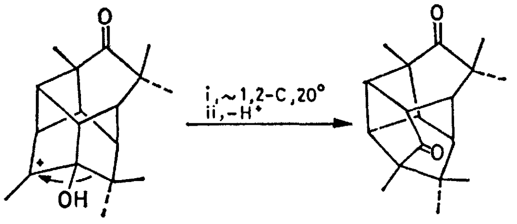
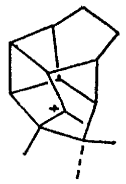
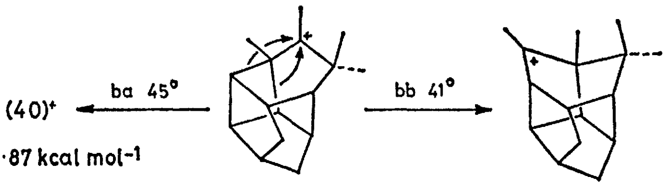
* In order to locate the paths which lead potentially to (31) or (35), we nevertheless studied the consequences of the isomerization of $(38)^+$, the product from path *b*. It gives a diketone (33). Comparison of $\Delta\Delta H_f$ values of hydrocarbon models of (33), 7.14 for $(33)^+$, and 12.97 kcal mol⁻¹ for $(33')^+$, indicates that the ' upper ' carbonyl group will be protonated faster than the ' lower ' carbonyl. Among the six possibilities of 1,2-alkyl shifts in $(33)^+$, two paths ba and bb appear favourable leading to products having negative $\Delta\Delta H_f$ values. Since their orbital alignment factors are almost equal, path ba will be favoured over path bb and it eventually gives (30) [equation (9)]. Path bb leads to (35) by way of $(42)^+$.



$(38)^+$ (33)



$(33')^+$



$\Delta\Delta H_f$ -4·87 kcal mol⁻¹

$(33)^+$ $(42)^+$

$\Delta\Delta H_f$ -0·88 kcal mol⁻¹

pathway from (29) to (30) is the four-step route indicated by the thick line in Figure 1. This route is identical with that proposed by Hirao [21] on rather intuitive grounds and characterized by remarkably low $\Delta\Delta H_f$ values calculated for the key intermediates $(37)^+$ and $(40)^+$ relative to their counterparts, $(38)^+$ and $(41)^+$, respectively. Hirao [21] argued that greater stability of $(37)^+$ relative to $(38)^+$ derives from the fact that a six-membered ring (thick line, Figure 2) of $(37)^+$ containing an ionic centre can take the relatively strain-free chair form whereas the corresponding six-membered ring in $(38)^+$ must be a deformed chair in the constrained molecular framework. While this argument is certainly correct as judged by the calculated dihedral angles along the rings (Figure 2),* our analysis suggests that the four-membered ring, of which these molecules each contain one, may also be responsible. The calculated steric energy sum at each non-methyl carbon atom † (Figure 2) reveals a high concentration of strain in the four-membered ring, that of $(37)^+$ being clearly less strained than that of $(38)^+$: the latter has narrower endocyclic angles (82—85°) and is more deeply puckered (dihedral angle 35°) than the former (85—90° and 23°).

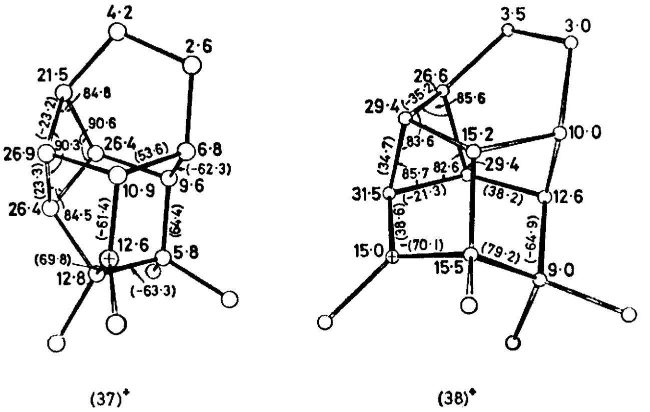


FIGURE 2 Calculated strain distribution (kcal mol^{-1}), dihedral ( ) and valence angles in four-membered ring, and dihedral angles [ ] in six-membered ring containing ionic centre of tetramethylpentacyclododecyl cations, $(37)^+$ and $(38)^+$, models of key intermediates in the acid-catalysed rearrangements of (29)

The origin of the difference in the total steric energies of $(40)^+$ and $(41)^+$ is difficult to assign, since the steric energy distribution in these molecules, which have only five- and six-membered rings, is more uniform (Figure 3) than in the previous pair. Nevertheless, angle bending strain appears to be responsible for the higher energy at every non-methyl carbon atom of $(41)^+$ compared with the corresponding atom of $(40)^+$.‡

Let us proceed to the next problem: why is (30) in such a deep local energy minimum that it cannot isomerize further into the thermally more stable (31) or (35) under ordinary conditions? In a hydrocarbon cation $(41)^+$ which should be regarded as a model of protonated (30), three 1,2-alkyl shift possibilities exist (Scheme 3). According to our criteria, by far the most favourable route is path aea, which leads to $(40)^+$ which eventually gives back (30) [equation (9)]. In other words, protonation of (30) is most likely to result in degenerate isomerization always reproducing the same structure (30). The other possibilities of reaching (31) or (35) from the neighbourhood of (29), (30), or (32) involve taking path af or be, both of which, however, are considered unfavourable as mentioned above.

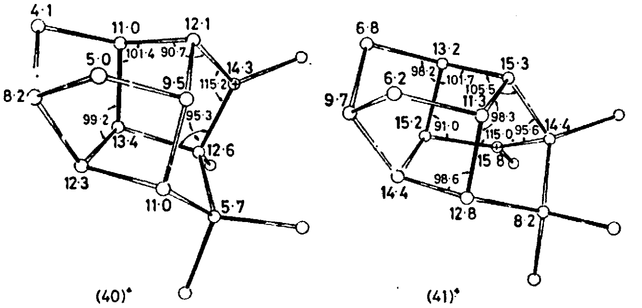
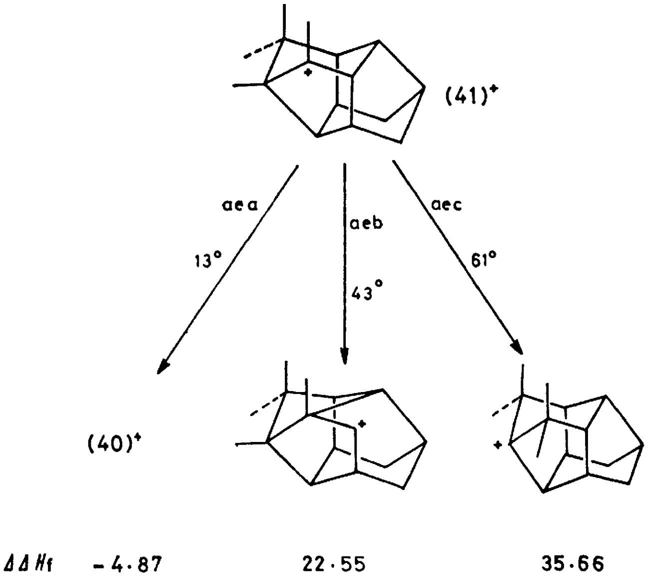


FIGURE 3 Calculated strain distribution (kcal mol^{-1}), and some valence angles of tetramethylpentacyclododecyl cations, $(40)^+$ and $(41)^+$, models of key intermediates in the acid-catalysed rearrangements of (29)

Conclusions.—The present analysis of the reported reactions of strained cage molecules indicates that force field calculations are helpful in interpreting observed effects of steric origin. If used judiciously, such calculations should be a remarkably effective tool in organic



SCHEME 3

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* The 'normal' endocyclic dihedral angle of cyclohexane is 54.9°.[24]

† The steric energy components between atoms pairs initially calculated by the molecular mechanics program are mechanically partitioned as in bond strain. See ref. 1 for details.

‡ Careful strain analysis of parent hydrocarbon pairs (A) and (B) (see footnote ‡ on p. 187) indicate that both can be regarded as two noradamanatane molecules fused together in different ways. In (A) the fusion increases the combined strain whereas that in B decreases it. Details of the analysis will be described elsewhere.

chemistry in understanding and even predicting the course of reaction and product distribution.

We thank Professor P. v. R. Schleyer for a copy of program STRAIN. Calculations were performed at Hokkaido University Computing Center, Kao Soap Company, Ltd., Mitsubishi Chemical Industry Company, Ltd., and The Hokkaido Takushoku Bank, Ltd. The generous donation of computer time by the two latter enterprises is gratefully acknowledged.

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