

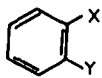
## THE CONFORMATIONAL BEHAVIOUR OF SOME MEDIUM-SIZED RING SYSTEMS

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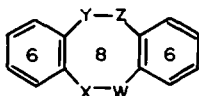
(Received 14 March 1974)

### INTRODUCTION

The work discussed in this paper originates from the so-called "rigid-group principle"<sup>1,2</sup> which recognised that the incorporation of torsionally rigid groups, such as the *ortho*-disubstituted benzene unit (1), into acyclic precursors encouraged, for statistical reasons, the formation of compounds containing medium and large rings. This approach led some years ago<sup>1</sup> to the synthesis and recognition of a number of 8-membered, 12-membered and larger ring systems and generated interest in the conformations of compounds of this type.



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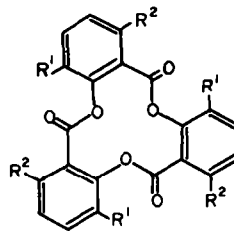


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The possible conformations of 8-membered ring systems of the '6,8,6' type (2), which include two "rigid groups", were first discussed<sup>3</sup> in 1935. These early ideas were used<sup>4</sup> to account for the existence of  $\alpha$ - and  $\beta$ -disalicylides (2, X=Z=O; Y=W=CO). Although this proposal<sup>4</sup> was later shown<sup>5</sup> to be incorrect, the idea<sup>3</sup> of two possible conformations for other '6,8,6' systems remained valid. The possible conformational behaviour of 5,6,11,12 - tetrahydrodibenzo[*a,e*]cyclo-octene (2, W=X=Y=Z=CH<sub>2</sub>) was described in detail in 1945 in a pioneering paper by Baker, Banks, Lyon, and Mann.<sup>16</sup> Their discussion based upon molecular models clearly indicated the possibility of a rigid chair-like conformation and a flexible boat-like conformation.

Our interest in the use of NMR line-shape methods<sup>†</sup> for the investigation of the dynamics of conformational changes led us first to re-examine the trisalicylide problem.<sup>6</sup> A proposal for the full

conformational itinerary for the 12-membered ring system of the trisalicylide derivatives (3) could then be put forward. In particular we were able to establish with certainty that these compounds (3) adopted propeller (C<sub>3</sub>) and helical (C<sub>i</sub>) conformations. However, a quantitative discussion of these



3a: R<sup>1</sup> = R<sup>2</sup> = Me

3b: R<sup>1</sup> = Me, R<sup>2</sup> = <sup>i</sup>Pr

3c: R<sup>1</sup> = <sup>i</sup>Pr, R<sup>2</sup> = Me

results in terms of relative conformational energies remains a future objective. In view of the rapid accumulation of information in the literature<sup>7</sup> on the kinetics of conformational change at the time (1968) that our investigations of the trisalicylide system were carried out, and the general absence of a quantitative assessment of the results, we decided to investigate compounds for which both an NMR line-shape examination and a molecular mechanics approach<sup>8</sup> to conformational energies could be attempted. The '6,8,6' system (2) was selected as our first objective in this comparative study which we then hoped to be able to extend subsequently to more complex systems. In order to carry out molecular mechanics calculations with confidence the compounds studied were, in part, restricted to those in which (i) the aromatic rings have either hydrogen or methyl substituents, and (ii) the torsionally mobile bridging groups (2, X-W and Y-Z) are associated with either C-C single bonds or double bonds, or contain heteroatoms that are not conjugated with the aromatic  $\pi$ -electron systems.<sup>‡</sup>

<sup>†</sup>In this paper we refer to only <sup>1</sup>H NMR spectra at 100 MHz.

<sup>‡</sup>For a promising way of overcoming these restrictions see Ref 9.

### The calculation of conformational energies

It is possible, in principle, to calculate the relative energies of different conformations using quantum mechanical methods. However, in practice, this has only been done successfully for small molecules and the results provide less insight for the organic chemist than those obtained by the much less laborious molecular mechanics calculations.<sup>6</sup> These methods for calculating relative strain energies have been used since the 1940's<sup>10</sup> but it was not until after the appearance of Hendrickson's classical paper<sup>11</sup> in 1961 that the wide scale introduction of computing techniques into organic chemistry led to the development of the method by a number of different groups.<sup>8</sup> In an important and recent critical review<sup>6a</sup> of this approach, it has even been concluded that molecular mechanics methods are preferable to the usual experimental methods for obtaining new enthalpy data for saturated hydrocarbons!

The compounds discussed in this paper present difficulties for molecular mechanics calculations on account of their complexity (30–66 atoms) and also because they include structural features, such as benzene rings and hetero-atoms, that require the use of strain energy parameters that are not as well tested as those that have been used for saturated hydrocarbons. The strain energy minimisation procedure that we have used was originally based upon the "steepest descent" method of Wiberg,<sup>12</sup> but it was subsequently found that the procedure reported by Allinger, Tribble, Miller and Wertz<sup>13†</sup> is much more efficient for the type of compound that we have studied. The major disadvantage of this<sup>13</sup> and related<sup>8</sup> methods is that it proves to be relatively inefficient for optimising the torsional strain in long polymethylene chains in cyclic or acyclic compounds. It may, however, be possible to overcome this problem by using modified torsional strain energy functions at an early stage in the calculation. This belief is probably well-based since it is found that excess torsional strain is effectively removed from multiple bonds presumably as a result of the much larger force constants,  $k_r$ , that are appropriate for these bonds (cf Table 1).


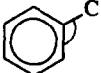
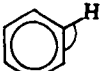
Our original choice of a force field was based upon that used by Boyd<sup>14</sup> for the calculation of strain energies of cyclophanes. There may well be imperfections in this force field, particularly when large angle deformations are involved (see below), but reasonably satisfactory results have now been obtained in a substantial number of calculations. Details of the force field used in our calculations are given in Table 1. The bond stretching force constant,  $k_r$ , and equilibrium values for bond lengths are not critical since bond stretching defor-

Table 1. Force field used for strain energy calculations

Bond stretching $E_R = 0.5 k_R (r - r_0)^2$			
Bond	$k_R$ kcal $\text{\AA}^{-2}$ mole <sup>-1</sup>	$r_0$ $\text{\AA}$	
C-H	655	1.09	
C-C	663	1.54 <sup>a</sup> , 1.52 <sup>b</sup> , 1.50 <sup>c</sup>	
C=C	1102	1.395	
(Aromatic)			
C-H	729	1.09	
(Aromatic)			
C-S	463	1.80	
C-N	716	1.472	
C=C	1397	1.337	

<sup>a</sup>In polymethylene chains. <sup>b</sup>C-C=. <sup>c</sup>C-Ar.

Angle deformation $E_\theta = 0.5 k_\theta (\theta - \theta_0)^2$		
Angle	$k_\theta$ kcal rad. <sup>-2</sup> mole <sup>-1</sup>	$\theta_0$ radians
C $\hat{C}$ C	115	1.94604
C $\hat{C}$ H	94	1.91113
H $\hat{C}$ H	74	1.88494
C $\hat{S}$ C	100	1.72613
C $\hat{C}$ S	115	1.94604
H $\hat{C}$ S	89	1.91113
C $\hat{N}$ C	144	1.90241
C $\hat{C}$ N	130	1.94604
H $\hat{C}$ N	100	1.91113
C=C-C	144	2.09439
C=C-H	94	2.09439
Aromatic 	144	2.09439
	144	2.09439
	108	2.09439



  

Torsion $E_\phi = 0.5 k_\phi (A + \cos n\phi)$			
Bond	$k_\phi$ kcal mole <sup>-1</sup>	A	n
C-C	3.0	1	3
C-S	2.1	1	3
C-N	4.4	1	3
C-C (=C)	-2.0	-1	3
C=C <sup>a</sup>	-16.0	-1	2
C=C			
(Aromatic)	-11.5	-1	3

<sup>a</sup>For each  $\text{>C=C<}$   $E_\phi$  is summed over all four torsion angles, corresponding to a torsional barrier of 64 kcal mole<sup>-1</sup>.

†We thank Professor N. L. Allinger for kindly communicating details of this procedure to us.

Table 1—Continued

Out-of-plane deformation	$E_{\Delta} = 0.5 k_{\Delta} \Delta^2$		
	$k_{\Delta}$ kcal rad. <sup>-2</sup> mole <sup>-1</sup>		
	100		
	40		
Non-bonded interactions $E_{\text{NBI}}^{\dagger} = A e^{-(r/0.776B)} - C(B/r)^6$			
Interaction	A	B <sup>b</sup>	C
C,C	88600	3.4	0.241
H,C	55500	2.9	0.153
H,H	34800	2.4	0.095
C,S	151500	3.55	0.412
H,S	95200	3.05	0.259
C,N	82800	3.2	0.225
H,N	52200	2.7	0.142

<sup>†</sup> $E_{\text{NBI}}$  in kcal mole<sup>-1</sup>,  $r$  in Å. This corresponds to the Hill Function (Ref 16).

<sup>b</sup>Corresponding to the following van der Waals radii (Å): C, 1.7; H, 1.2; S, 1.85; N, 1.5.

For force constants and equilibrium geometries of sulphides see: J. H. Carter, J. M. Freeman, and T. Henshall, *J. Mol. Spec.* **22**, 18 (1967); D. W. Scott and M. Z. El Sabban, *J. Mol. Spec.* **30**, 317 (1969); H. Siebert, *Z. Anorg. Allgem. Chem.* **271**, 65 (1952); **273**, 161 (1953).

For amines see: D. R. Lide, *J. Chem. Phys.* **27**, 343 (1957); **28**, 572 (1958); G. Dellepiane and G. Zerbi, *J. Chem. Phys.* **48**, 3573 (1968); J. Stackhouse, R. D. Baechler, and K. Mislow, *Tetrahedron Letters* 3437 (1971).

For alkenes see: G. Favini, G. Buemi, and M. Raimondi, *J. Mol. Struct.* **2**, 137 (1968); **3**, 385 (1969); N. L. Allinger and J. T. Sprague, *J. Am. Chem. Soc.* **94**, 5734 (1972).

mation is not dominant in determining conformational strain energies: the equilibrium values and force constants,  $k_{\Delta}$ , for angle deformation are much more critical. The method that we have employed for evaluating angle strain energy,  $E_{\Delta}$ , is not entirely satisfactory since it tends to over-estimate angle strain for large angle deformations. We have attempted to deal with this problem by a rather arbitrary reduction of force constant values for large

angle deformations (*cf* Ref 13). However, more satisfactory solutions may lie in the use of a Urey-Bradley force field or of a modified function<sup>8</sup> for  $E_{\Delta}$ . Stretch-bend interactions<sup>13</sup> are not included in our treatment since we are more interested in relative conformational energies than in the accurate reproduction of bond lengths. The torsional and non-bonded interaction functions that we have used are chosen so that rotational barriers<sup>15</sup> are largely due to the relative values of  $E_{\Delta}$  (see Table 1). This results from our choice of the Hill Function<sup>16</sup> for estimating non-bonded interactions and also the use of relatively small van der Waals radii. This approach reproduces energy barriers for conformational changes in cyclophanes, where non-bonded interactions are important, but it does not reproduce, for example, axial-equatorial energy differences for substituted cyclohexanes which are underestimated by our procedure. Out-of-plane deformation energy in aromatic rings,  $E_{\Delta}$ , is estimated by using the approach put forward by Boyd,<sup>14</sup> and this also gives good results when applied to conformational changes in cyclophanes.

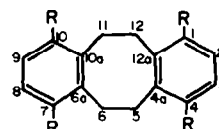
#### The conformational behaviour of some '6,8,6' systems

5,6,11,12-Tetrahydrodibenzo[a,e]cyclo-octene (4) and analogous compounds.<sup>17</sup> At the start of this work the conformation of both 1,5-cyclo-octadiene and its dibenzo-derivative (4) were not firmly established although interest had been expressed in the problem over many years. On both geometrical grounds<sup>18</sup> and from the examination of models (*cf* Ref 1) it is clear that both a rigid chair-like conformation and a family of flexible boat-like conformations are possible for 1,5-cyclo-octadiene and its dibenzo-derivative (4). Dipole moment measurements<sup>19</sup> and early NMR studies suggested that 1,5-cyclo-octadiene predominantly adopts a twist-boat conformation in solution: these conclusions are consistent with recent crystallographic results<sup>20</sup> and an NMR study.<sup>21</sup>

The NMR spectrum<sup>17</sup> of the hydrocarbon (4) in CDCl<sub>3</sub>-CS<sub>2</sub> shows clearly, at low temperatures, two sets of aromatic proton signals and two sets of methylene proton signals which are assignable to two conformations present in approximately a 1:1 ratio. The rate of interconversion of the two conformations may be obtained from the temperature dependence of the aromatic proton signals which coalesce to a singlet at higher temperatures. The appearance of the methylene proton signals is more revealing. One conformation gives a singlet signal, consistent with a rapidly inverting flexible conformation, and the second conformation gives an AA'BB' system assignable to a conformation that is rigid on the NMR time scale.† From the examination of models and from molecular mechanics calculations, the rigid conformation is

†The results obtained in our study<sup>17</sup> agree with those recently reported<sup>22</sup> for an independent examination of the hydrocarbon (4); the second study extends the results reported here to the measurement of the activation energy for the process Boat $\rightleftharpoons$ Boat\*.

clearly the Chair<sup>†</sup> conformation (6) and the mobile conformation belongs to a family of Boat<sup>†</sup> conformations. These results provide satisfying support for the conformational scheme outlined in Fig 1.‡ The scheme considers the general conformational situation for the hydrocarbon (4) and analogues (2) in which one or more of the ring methylene groups are replaced by suitably substituted heteroatoms. Conformations are conveniently described using the usual notation for torsional angles (see 5 and Refs 11 and 23) and referring in turn to the 4a-5, 5-6, 6-6a, 10a-11, 11-12, and 12-12a bonds. The conformations C and C\* (6) are related, in terms of



4: R = H  
11: R = Me



5: Notation for torsional angles

†In this paper the descriptions "Chair" and "Boat" are not specific. "Chair" refers to the conformations C and C\* and "Boat" to any of the infinite number of conformations lying on the pseudorotational itinerary  $B \rightleftharpoons TB \rightleftharpoons B^* \rightleftharpoons TB^* \rightleftharpoons B$  (see Fig 1).

‡In Fig 1, and similar figures in this paper, conformational diagrams are restricted to one of each type, e.g. C (6). This and related conformations, e.g. C\* (6), are listed below each diagram in terms of the appropriate torsional angles.

the NMR spectrum, by geminal site exchange of the methylene group protons, and for chiral systems C and C\* are also related as enantiomers. Other pairs of conformations, B and B\* etc., are related in a similar way.

There are a number of possible transition states for the interconversion of the various conformations shown in Fig 1, and a few well defined high-

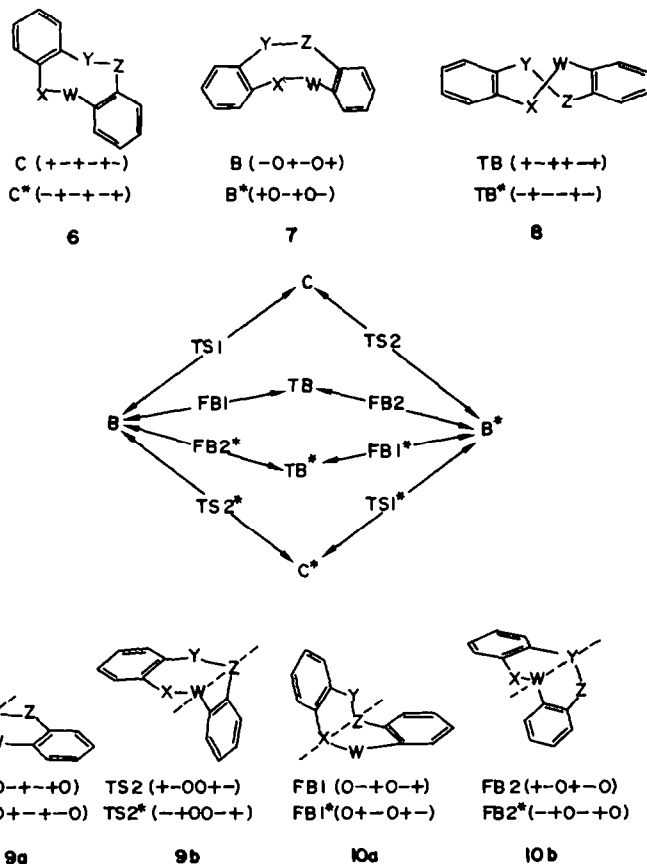


Fig 1. Conformational changes of 5,6,11,12-tetrahydrodibenzo[a,e]cyclo-octene (4) and heterocyclic analogues. The notation for torsional angles (5) refers in turn to the 4a-5, 5-6, 6-6a, 10a-11, 11-12, and 12-12a bonds (see 4).

energy conformations were selected so that the measured activation energy for the conformational change, Chair $\rightleftharpoons$ Boat, could be compared with calculated activation energies. In particular the conformation TS1 (9) [for the hydrocarbon (4) W=X=Y=Z=CH<sub>2</sub> and TS1 $\equiv$ TS1\* $\equiv$ TS2 $\equiv$ TS2\*],<sup>†</sup> characterised by the coplanarity of C atoms 4a, 5, 6, 11, 12, and 12a, was examined as a likely transition state for the process Chair $\rightleftharpoons$ Boat. The conformation FB1 (10) (for 4, W=X=Y=Z=CH<sub>2</sub>, FB1 $\equiv$ FB2 and FB1\* $\equiv$ FB2\* are related as enantiomers) was considered as a probable high energy point on the pseudorotational itinerary of the Boat conformations since it is characterised by the coplanarity of atoms 4a, 5, 6, 12, and 12a, with consequently maximised non-bonded transannular interactions between the pair of methylene groups at C-6 and C-12. The minimum energy boat conformation (MEB) could be related to either the B(7) or TB(8) conformational types, but on the basis of calculations the minimum energy conformation of the hydrocarbon (4) is characterised by torsional angles of ca +26° about the 5-6 and 11-12 bonds. It is therefore situated geometrically between B(7) and FB1 (10) in the conformational itinerary depicted in Fig 1 (with three other minimum energy conformations associated with three equivalent positions in this itinerary).

The calculated strain energies of the various conformations of the hydrocarbon (4) are summarised in Table 2. The strain energy differences between the conformations C $\equiv$ C\* (6) and TS1 $\equiv$ TS1\* $\equiv$ TS2 $\equiv$ TS2\* (9) ( $\Delta E_s$  11.5 kcal mole<sup>-1</sup>) is in satisfying agreement with the observed activation energy for the process Chair $\rightleftharpoons$ Boat ( $\Delta G^\ddagger$  10.2 kcal mole<sup>-1</sup>). We therefore conclude that the pathway C $\rightleftharpoons$ TS1 $\rightleftharpoons$ B is a reasonable representation of

this process. The barrier to the pseudorotational process that interconverts the minimum energy boat conformations probably involves the transition state FB1 $\equiv$ FB2, FB1\* $\equiv$ FB2\* (10) although the calculated strain energy difference between these conformations ( $\Delta E_s$  4.5 kcal mole<sup>-1</sup>) is rather smaller than the observed activation energy<sup>22</sup> for the process Boat $\rightleftharpoons$ Boat\* ( $\Delta G^\ddagger$  7.5  $\pm$  1 kcal mole<sup>-1</sup>). These conclusions have recently been supported<sup>25</sup> by a similar examination of the conformational behaviour of 1,4,7,10-tetramethyl-5,6,11,12-tetrahydrodibenzo[a,e]cyclo-octene (11). The methyl substituents give two signals at low temperature assignable to Chair and Boat conformations and the free energy of activation associated with the coalescence of these two signals ( $\Delta G^\ddagger$  11.8 kcal mole<sup>-1</sup>) agrees well with the calculated strain energy difference of the C(6) and TS1 (9) conformations (see Table 2,  $\Delta E_s$  13.2 kcal mole<sup>-1</sup>).

In all of the strain energy calculations summarised in Table 2 the values of the bond bending force constants,  $k_b$ , have been reduced since large angle deformations are involved in the conformation TS1. The reduction is probably inconsistent with angle deformation strain associated with small angle deformations (see below). If normal values for force constants are used, the calculated energy barriers for (4) become approximately 17.6 kcal mole<sup>-1</sup> ( $\Delta E_s$  for C and TS1) and 7.6 kcal mole<sup>-1</sup> ( $\Delta E_s$  for minimum energy Boat and FB1). The observation of an equilibrium between Chair and Boat conformations for the hydrocarbons (4 and 11) is of interest since the crystal structure of the dibenzoderivative (4) is consistent<sup>1</sup> with a centrosymmetric conformation, presumably C $\equiv$ C\* (6), in the solid state. On the other hand, the NMR spectra of derivatives of 4 have been interpreted<sup>24</sup> in terms only of a boat-like conformation.

The replacement of one or more of the CH<sub>2</sub> groups (W, X, Y, Z in 6-10) of the hydrocarbon (4) by S, SO<sub>2</sub>, N-acyl or N-toluenesulphonyl

Table 2. Strain energies<sup>a</sup> of selected conformations of 5,6,11,12-tetrahydrodibenzo[a,e]cyclo-octene (4) and its 1,4,7,10-tetramethyl-derivative (11)

Conformation	Hydrocarbon (4)						Hydrocarbon (11)					
	$E_s$	$E_R$	$E_\theta$	$E_\bullet$	$E_\Delta$	$E_{NBI}$	$E_s$	$E_R$	$E_\theta$	$E_\bullet$	$E_\Delta$	$E_{NBI}$
C $\equiv$ C* (6)	6.45	0.02	0.69	5.59	0.01	0.14	7.31	0.05	1.18	5.95	0.13	0.00
B $\equiv$ B* (7)	7.50	0.08	0.98	6.00	0.01	0.43	7.96	0.11	1.66	6.00	0.15	0.04
TB $\equiv$ TB* (8)	7.46	0.02	0.89	6.04	0.07	0.44	9.26	0.20	1.86	6.10	0.07	1.03
MEB	6.69	0.10	0.35	3.72	0.63	1.89	5.97	0.08	1.62	4.05	0.22	0.00
TS1 $\equiv$ TS1* $\equiv$ TS2 $\equiv$ TS2* (9)	17.90	0.62	15.05	0.06	0.04	1.23	20.54	0.87	16.88	0.93	1.05	0.81
FB1 $\equiv$ FB2, FB1* $\equiv$ FB2* (10)	11.18	0.28	8.35	1.20	0.07	1.28						

<sup>a</sup> All strain energies in kcal mole<sup>-1</sup>.

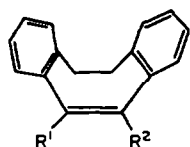
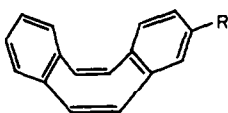
<sup>b</sup> Conformations retaining plane of symmetry ( $C_{2h}$  and  $C_{2v}$ ).

<sup>c</sup> Conformation retaining axis of symmetry ( $D_2$ ).

<sup>d</sup> Defined by coplanarity of atoms 11, 12, 12a, 4a, 5, and 6 (C<sub>1</sub>).

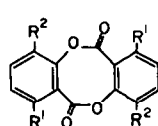
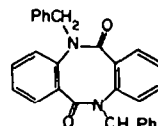
<sup>e</sup> Defined by coplanarity of atoms 12, 12a, 4a, 5, and 6 (C<sub>2</sub>).

results in changes in (i) the Chair $\rightleftharpoons$ Boat equilibrium and (ii) the activation energies for conformational changes of the type shown in Fig 1. These structural changes introduce considerable difficulty into possible strain energy calculations. The results so far obtained experimentally in this series have already been discussed<sup>17</sup> in detail.

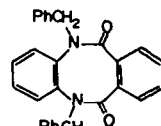
12a: R<sup>1</sup> = R<sup>2</sup> = H12b: R<sup>1</sup> = Me, R<sup>2</sup> = H12c: R<sup>1</sup> = R<sup>2</sup> = Me

13

180° (AB system from CH<sub>2</sub>Ph methylene protons). This is to be expected since a combination of steric effects associated with the N-benzyl substituents and the conjugative demands of the *cis*-amide linkages combine to produce a high degree of conformational rigidity ( $\Delta G^\ddagger$  for inversion > 27 kcal mole<sup>-1</sup>).

14a: R<sup>1</sup> = Me, R<sup>2</sup> = Pr'14b: R<sup>1</sup> = Pr', R<sup>2</sup> = Me

15



16



17

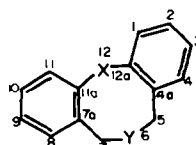
The conformational situation for compounds of the '6,8,6' type analogous to 4 is changed considerably when further multiple bonds are introduced into the 8-membered ring. Thus molecular models show that both 5,6-dihydrodibenzo[*a,e*]cyclo-octene (12) and dibenzo[*a,e*]cyclo-octene (13, R=H) can adopt only the boat-like conformations shown. The conformational mobility of derivatives of 12 can be studied<sup>26</sup> by NMR methods since the -CH<sub>2</sub>-CH<sub>2</sub>- group gives rise to an AA'BB' system for slow ring-inversion and an A<sub>4</sub> system for fast ring-inversion on the NMR time scale. The NMR spectrum of the unsubstituted hydrocarbon (12a) is unchanged (CH<sub>2</sub>-CH<sub>2</sub> singlet) down to -110°, but the spectrum of the monomethyl derivative (12b) shows a complex ABCD system for the -CH<sub>2</sub>-CH<sub>2</sub>- group which coalesces to a singlet above -40°. The accurate value of the inversion barrier for 12b has not been calculated due to the complexity of the NMR spectrum, but it is obviously much higher than that for the parent (12a) and much lower than that for the dimethyl derivative (12c) which shows an AA'BB' system for the CH<sub>2</sub>-CH<sub>2</sub> group up to 200°. Inversion barriers in the dibenzocyclo-octatrienes (12) are therefore highly dependent upon the substituents R<sup>1</sup> and R<sup>2</sup>.

The inversion barriers found<sup>27</sup> for a derivative of the hydrocarbon (13, R = CF<sub>2</sub>H;  $\Delta G^\ddagger$  12.3 kcal mole<sup>-1</sup>) is higher than that likely to be associated with the cyclo-octatriene derivative (12a). This system also shows pronounced substituent effects.<sup>27,28</sup>

In view of the above results for the hydrocarbons (4, 11, 12, and 13) and their derivatives, it is gratifying that the disalicylide derivatives (14) also show temperature dependent NMR spectra associated with a considerable barrier to inversion of their boat-like conformations<sup>29</sup> (14a:  $\Delta G^\ddagger$  17.7 kcal mole<sup>-1</sup>, and 14b:  $\Delta G^\ddagger$  18.4 kcal mole<sup>-1</sup>). On the other hand, compounds such as the bis-lactams (15 and 16) show no change in their NMR spectra up to

Whereas inversion of the boat-like conformation of the cyclo-octatriene derivatives (13) probably involves a planar transition state, the cyclo-octatriene derivatives (12) have additional torsional freedom about the CH<sub>2</sub>-CH<sub>2</sub> bond: the transition state for inversion is likely to be as shown in 17 in which the saturated bridge adopts a staggered conformation. The disalicylides (14) have restricted torsional freedom about the *cis*-ester linkages as a result of p- $\pi$  conjugative interaction, but it is thought likely that the inversion of their boat-like conformations follows more closely the conformational itinerary B $\rightleftharpoons$ TB $\rightleftharpoons$ B\* $\rightleftharpoons$ TB\* $\rightleftharpoons$ B, (cf Fig 1) involving transition states of the FB1 and FB2 type (cf 10). Thus the disalicylide derivatives (14) probably follow conformational pathways associated with ring systems analogous to the cyclo-octadiene derivative (4) rather than those followed by cyclo-octatriene (12) and cyclo-octatetraene (13) derivatives. A quantitative assessment of inversion barriers in compounds of the disalicylide (14) and bis-lactam (15 and 16) types cannot be made using molecular mechanics calculations until the problem of assigning suitable force constants for groups such as Ar-N-CO-Ar, Ar-O-CO-Ar, and Ar-C=C-Ar has been satisfactorily surmounted.

5,6,7,12-Tetrahydrodibenzo[*a,d*]cyclo-octene and analogous compounds (18).<sup>30</sup> In view of the ex-

18a: X = Y = CH<sub>2</sub>18b: X = CH<sub>2</sub>, Y = S18c: X = CH<sub>2</sub>, Y = NCH<sub>2</sub>Ph18d: X = CH<sub>2</sub>, Y = NMe

18e: X = CO, Y = NMe

tremely satisfactory results obtained for the dibenzo[*a,e*]cyclo-octene derivatives (4 and 11), it was of interest to extend our studies to include an examination of the conformational changes of the closely related dibenzo[*a,d*]cyclo-octene derivatives (18). An examination of models of the hydrocarbon (18a) shows that, as for cyclo-octa-1,4-diene, there is a rigid Chair conformation (19) and a flexible Boat conformation (20, 21). In this case the Boat conformation (20) does not have the symmetry required<sup>18</sup> for complete pseudorotation ( $B \rightleftharpoons TB \rightleftharpoons B^* \rightleftharpoons TB^* \rightleftharpoons B$ ) without the introduction of angle strain. However, the strain introduced is small (see Table 3) and for practical purposes this Boat conformation (20) may be considered to undergo pseudorotation in much the same way as the Boat conformation of 4. The hydrocarbon (18a) is a rather inconvenient molecule to study by NMR line shape methods due to the anticipated complexity of the NMR spectrum of the  $CH_2-CH_2-CH_2$  group. We have therefore focussed our attention entirely upon heterocyclic analogues of 18 and in two cases (18b and 18d), these have also proved

suitable for comparison with calculated strain energies.

In general, the dibenzo-derivatives (18) show NMR spectra at room temperature, or above, consistent with rapid conformational changes (C-5 and C-7 methylene protons as a single singlet signal). At lower temperatures, however, changes are observed in their NMR spectra which in most cases are consistent with an equilibrium involving two conformational species. One of these is a rigid conformation (AB system from C-5 and C-7 methylene protons), readily assignable to a chair-like conformation, C and C\* (19). The other is a flexible conformation (singlet from C-5 and C-7 methylene protons) which evidently lies on the pseudorotational itinerary  $B \rightleftharpoons TB \rightleftharpoons B^* \rightleftharpoons TB^* \rightleftharpoons B$  (see Fig 2). In the cases of the two compounds (18b and 18a) studied by strain energy calculations (Table 3), the observed energy barrier to the conformational change Boat  $\rightleftharpoons$  Chair is consistent with a transition state of the type TS1 (22) ( $C_1$  symmetry, atoms 4a, 5, 6, 12, and 12a coplanar), rather than the other two possible transition states

Table 3. Strain energies of selected conformations of 5,7-dihydro-12H-dibenzo[*c,f*]thiocin (18b) and 6-methyl-5,6,7,12-tetrahydrodibenz[*c,f*]azocine (18d)

Conformation	Thiocin derivative (18b)						Azocine derivative (18d)					
	$E_s$	$E_R$	$E_o$	$E_o^*$	$E_\Delta$	$E_{NB1}$	$E_s$	$E_R$	$E_o$	$E_o^*$	$E_\Delta$	$E_{NB1}$
C $\equiv$ C** (19)	1.87	0.15	1.18	1.95	0.04	-1.45	4.30	0.16	1.92	3.99	0.10	-1.88
B $\equiv$ B** (20)	9.67	0.35	7.70	0.48	0.12	1.03	5.94	0.20	3.84	2.83	0.17	-1.10
TB $\equiv$ TB** (21)	5.21	0.24	4.88	0.40	0.66	-0.97	5.62	0.33	5.48	0.17	0.26	-0.61
MEB <sup>c</sup>	5.10	0.24	2.60	2.21	0.12	-0.07						
TS1A $\equiv$ TS1B, TS1A* $\equiv$ TS1B** (22)	19.43	0.56	16.70	2.14	0.16	-0.12	22.58	0.68	17.04	4.57	0.07	0.23
TS3 $\equiv$ TS3** (24)	21.59	0.29	16.71	4.38	0.62	-0.41	27.29	0.33	16.20	9.52	1.94	-0.69
TS2 $\equiv$ TS2** (23)	33.27	0.75	27.90	3.79	0.08	0.75	33.36	0.57	23.87	8.36	0.01	0.56

<sup>a</sup> $C_1$  symmetry.

<sup>b</sup> $C_2$  symmetry.

<sup>c</sup> $\phi_{36} = 22.9^\circ$ ,  $\phi_{67} = 84.0^\circ$  for thiocin, undetermined for azocine.

<sup>d</sup>Defined by coplanarity of atoms 12a, 4a, 5, 6, and 7.

<sup>e</sup>Defined by coplanarity of atoms 4a, 5, 6, 7, and 7a;  $C_1$  symmetry.

<sup>f</sup>Defined by coplanarity of atoms 4a, 7a, 11a, 12, and 12a;  $C_1$  symmetry.

Table 4. Strain energies<sup>a</sup> of selected conformations of 5,7-dihydro-dibenzo[*c,g*]thionin (25c)

Conformation	$E_s$	$E_R$	$E_o$	$E_o^*$	$E_\Delta$	$E_{NB1}$
C $\equiv$ C** (28)	1.40	0.23	0.82	1.41	0.09	-1.16
B $\equiv$ B** (29)	9.18	1.20	4.42	0.78	0.80	1.97
DB1 $\equiv$ DB1** $\equiv$ DB2 $\equiv$ DB2** (31, 32)	6.24	0.94	3.45	0.93	0.14	0.79
TB $\equiv$ TB** (30)	14.09	2.32	13.92	-6.26	4.11	0.01
TS $\equiv$ TS** (33)	17.50	2.68	7.03	5.57	3.86	-1.64

<sup>a</sup>All strain energies in kcal mole<sup>-1</sup>.

<sup>b</sup>The torsional barrier associated with the C=C bond was treated as a two-fold barrier of height 65 kcal mole<sup>-1</sup>. Conjugation energy of 5 kcal mole<sup>-1</sup> for the double bond with each aromatic ring was also included in the calculations.

<sup>c</sup> $C_1$  symmetry.

<sup>d</sup> $\phi_{36} = +48^\circ$ ;  $\phi_{67} = -98^\circ$ .

<sup>e</sup> $C_2$  symmetry.

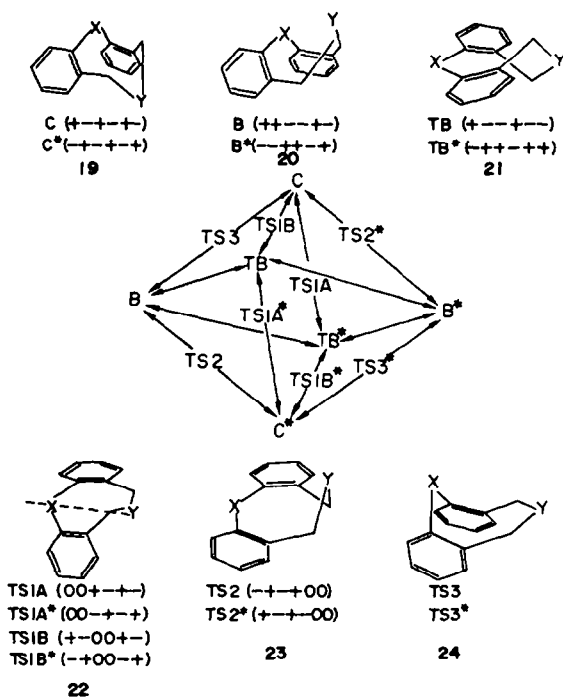


Fig. 2. Conformational changes of 5,6,7,12-tetrahydrodibenzo-[a,d]cyclo-octene and heterocyclic analogues. The notation for torsional angles ( $\theta$ ) refers in turn to the 4a-5, 5-6, 6-7, 7-7a, 11a-12, 12-12a bonds (see 18).

TS2 (23) (C, symmetry, atoms 4a, 7a, 11a, 12, and 12a coplanar) or TS3 (24) (C, symmetry, atoms 4a, 5, 6, 7, and 7a coplanar).

The observed free energies of activation for the process Chair $\rightleftharpoons$ Boat for both the thiocin derivative 18b ( $\Delta G^\ddagger$  16.2 kcal mole $^{-1}$ ) and the azocine derivative 18c ( $\Delta G^\ddagger$  17.4 kcal mole $^{-1}$ ) are in good agreement with the calculated strain energy differences between the C and TS1 conformations for both 18b ( $\Delta E_s$  17.6 kcal mole $^{-1}$ ) and the azocine derivative 18d ( $\Delta E_s$  18.2 kcal mole $^{-1}$ ). $\dagger$  This reasonable measure of agreement is once again only obtained by using reduced angle strain force constants (0.7  $k_a$ ) in the calculations.

The shape of the energy profile for pseudorotation of the Boat conformation clearly depends upon the substituents X and Y. On the basis of our strain energy calculations (Table 3) the energy profile is quite different for the compounds 18b and 18d. Thus for the thiocin derivative (18b) the minimum energy boat conformation (MEB) is reasonably well defined and lies closer to the C, TB conformation (21) than to the C, B conformation

(20). A minimum energy boat conformation could not be found for the azocine derivative (18d) and the strain energies of both B and TB types are rather similar (Table 3). Although results for other compounds of the type (18) have been obtained by NMR line-shape methods, it is unfortunately difficult to make comparisons with molecular mechanics results at the present time. This would require calculation of strain energies for compounds with X = O, S, NR etc. and this cannot be done convincingly due to potential p- $\pi$  conjugation between the group X and the aromatic rings in the compounds 18.

The NMR spectral data for the azocine derivative (18e) are different from the other members of the series (18) in that the results are consistent with the presence of only a single rapidly inverting conformation, even at  $-100^\circ$  (single signal for C-5 and C-7 methylene protons). The chemical shift data are consistent with this being a conformation of the boat type. This observation of a rapidly inverting Boat conformation for the compound 18e and the virtual absence, or near absence, of the chair conformation [ $\Delta G$  (C $\rightarrow$ Boat)  $< -2.3$  kcal mole $^{-1}$ ] is consistent with the replacement of the usual non-bonded interaction between X and Y in the B conformation (see 20) with a weakly attractive, or bonding, interaction since  $\Delta G^\ddagger$  (B $\rightleftharpoons$ B\*)  $< \sim 8$  kcal mole $^{-1}$ . This proposal (Fig 3) is reminiscent of the suggestion made some years ago $^{31}$  that in suitable medium-sized cyclic aminoketones there is an attractive transannular interaction between the nitrogen atom and the carbon atom of the carbonyl group (Fig 3).

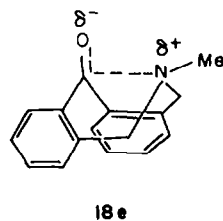


Fig. 3. Transannular electronic interaction in the cyclic aminoketone (18e).

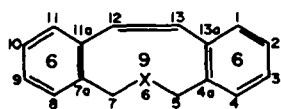
*The conformational behaviour of '6,9,6' and '6,10,6' systems* $^{32}$

The recognition that heterocyclic derivatives of '6,8,6' systems of the general type 2 and 18 exist in solution in diastereomeric Chair and Boat conformations (see Fig 1) encouraged us to extend $^{32}$  our investigations to include some related '6,9,6' systems (25 and 26) and '6,10,6' systems (27).

In those '6,9,6' systems which are heterocyclic analogues (25) of 12,13-dihydro-11H-dibenzo[a,e]cyclononene, similarities in conformational behaviour with that of the '6,8,6' systems (18) are observed. The temperature dependent NMR

$\dagger$ The calculation was carried out for the N-methyl derivative (18d) for simplicity. The N-Me group is not involved in important interactions in any of the conformations studied.

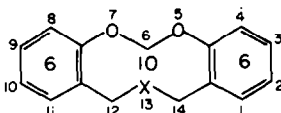




**25a:** X = NMe

**25b:** X = NCH<sub>2</sub>Ph

**25c:** X = S

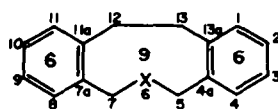


**27a:** X = NMe

**27b:** X = NCH<sub>2</sub>Ph

**27c:** X = S

**27d:** X = SO<sub>2</sub>



**26a:** X = NH

**26b:** X = NMe

**26c:** X = NCH<sub>2</sub>Ph

**26d:** X = NCOMe

**26e:** X = S

**26f:** X = SO<sub>2</sub>

spectra of the amines (**25a** and **25b**) demonstrate that two diastereomeric conformations are populated in solution. In each case at low temperatures, the C-5 and C-7 methylene protons exhibit (i) an AB system assignable to a relatively rigid conformation and (ii) a singlet associated with a rapidly inverting conformation. These signals coalesce to an AB system as the temperature is increased and then to a singlet at higher temperatures. Two exchange processes can therefore be identified by line-shape analyses. The flexible conformation constitutes the minor conformation, and in the case of the sulphide (**25c**) it is not observable by NMR spectroscopy where coalescence of a single AB system characterises the temperature dependent spectra. In the low temperature spectra of the amines (**25a** and **25b**) two singlets of unequal intensity are observed for the N-Me protons of **25a** and also for the methylene protons of the N-benzyl group in **25b**. The coalescence behaviour permits independent line-shape analysis of the interconversion processes involving the two diastereomeric conformations to be made. Agreement in both cases is excellent.

Examination of molecular models directed our attention (Fig 4) to five particular conformations: (i) a relatively rigid chair (C) conformation (**28**) with C<sub>1</sub> symmetry, (ii) a boat (B) conformation (**29**) with C<sub>1</sub> symmetry, (iii) a twist-boat (TB) conformation (**30**) with C<sub>2</sub> symmetry, (iv) asymmetric distorted-boat (DB) conformations (**31**) and (**32**), and (v) a transition state (TS) conformation (**33**) with C<sub>1</sub> symmetry. Strain energy calculations (Table 4) on the sulphide (**25c**) show that the C (**28**) and DB conformations (**31** and **32**) correspond to ground state conformations. The DB conformations (**31**, **32**) are situated geometrically between B (**29**) and TB (**30**) conformations in the conformational itinerary depicted in Fig 4 and are character-

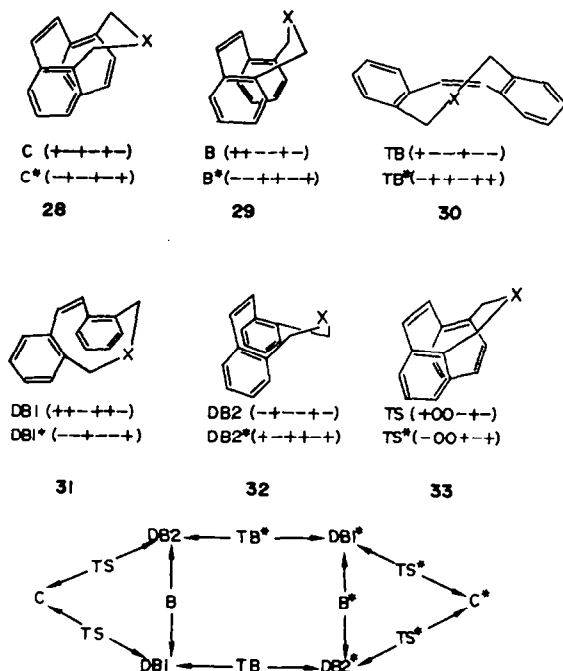


Fig 4. Conformational changes in the heterocyclic analogues of 12,13-dihydro-11H-dibenzo[a,e]cyclo-nene. The notation for torsional angles ( $\phi$ ) refers in turn to the 4a-5, 5-6, 6-7, 7-7a, 11a-12, and 13-13a bonds (see **25**).

ised by torsional angles of ca 45° and 98° about the 5-6 and 6-7 bonds respectively. The conformational itinerary associates the ground state conformations (C, DB1, DB2 and their enantiomeric or degenerate partners C\*, DB1\*, DB2\*) with the transition states (B, TB, TS and B\*, TB\*, TS\*). The TS conformation for Chair⇌Boat interconversion is characterised by coplanarity of atoms 4a, 5, 6, 7,

and 7a and thus has  $C_1$  symmetry. This situation contrasts with the transition state of  $C_1$  symmetry which was identified for 5,7-dihydro-12H-dibenzo[*c,f*]thiocin (18b) and 6-methyl-5,6,7,12-tetrahydrodibenz[*c,f*]azocine (18d). In the case of 5,7-dihydrodibenz[*c,f*]thionin (25c), the torsional rigidity associated with the olefinic double bond appears to be responsible for the preservation of  $C_1$  symmetry in the TS conformation (33). In the Boat family of conformations, the B conformation (29) is destabilised by transannular nonbonded interactions involving the sulphur atom, whereas the TB conformation (30) is characterised by large contributions to angle strain in the region of the olefinic double bond.

The observed free energy of activation ( $\Delta G^\ddagger = 15.5 \text{ kcal mole}^{-1}$ ) for  $C \rightleftharpoons C^*$  ring inversion in the thionin derivative (25c) is in very satisfying agreement with the calculated strain energy difference ( $16.1 \text{ kcal mole}^{-1}$ ) between the C and TS conformations (Table 4). The calculated strain energy difference ( $4.8 \text{ kcal mole}^{-1}$ ) between the C and DB conformations (Table 4) is consistent with the failure to observe any Boat conformation signals in the low temperature NMR spectrum of the thionin derivative (25c). The fact that both the N-Me azonin derivative (25a) ( $\Delta G^\ddagger 16.3 \text{ kcal mole}^{-1}$ ) and the N-benzyl azonin derivative (25b) ( $\Delta G^\ddagger = 16.1 \text{ kcal mole}^{-1}$ ) undergo  $C \rightleftharpoons C^*$  ring inversion via flexible boat conformations as detectable intermediates in their NMR spectra below  $0^\circ$  probably reflects the decreased destabilisation of the DB conformation (31, 32) when nitrogen replaces sulphur at position 6.

The '6,9,6' systems of the type 26 and the '6,10,6' systems (27) show<sup>32</sup> a completely different kind of conformational behaviour. At low temperatures the NMR spectra of the compounds 26b, 26c, 26e, and 26f show a single AB system associated with either homotopic or enantiotopic<sup>6c</sup> C-5 and C-7 methylene groups. This highly informative result requires that the observable ground state must have either  $C_1$  or  $C_2$  symmetry. A decision between these two possibilities is provided by the NMR spectrum of the N-benzyl derivative (26c), where below  $\sim 50^\circ$  the methylene protons of the benzyl group give rise to an AB system and are therefore demonstrably diastereotopic. Clearly, the ground state conformation of the '6,9,6' systems (26) must have  $C_2$  symmetry leading to either a  $C_2$  chair (34) or a  $C_2$

boat (35) as the only two possibilities. Discrimination in favour of the  $C_2$  chair (34) as the preferred conformation for the '6,9,6' systems (26) was provided by strain energy calculations (Table 5) on the sulphide (26e). We feel that extrapolation to the other '6,9,6' systems is justifiable and do not share the view<sup>33</sup> that the secondary amine (26a) has a "freely rotating ring system."

Examination of molecular models indicates that the  $C_2$  chair (34) is a flexible conformation and that ring inversion can occur by a pseudorotational process (Fig 5) involving  $C_1$  chair (36) conformations. The transition state geometry has not been characterised by strain energy calculations in this case,

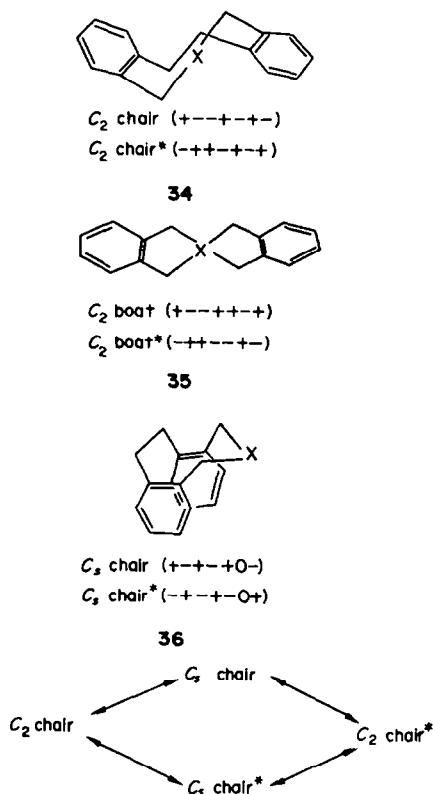


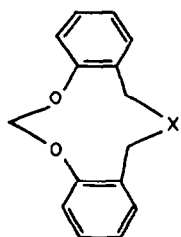
Fig 5. Conformational changes in the heterocyclic analogues (26) of 6,7,11,12-tetrahydro-5H-dibenzo[*a,e*]cyclononene. The notation (S) for torsional angles refers in turn to the 4a-5, 5-6, 6-7, 7-7a, 11a-12, 12-13 and 13-13a bonds.

Table 5. Strain energies\* of selected conformations of 5,7,12,13-tetrahydrodibenzo[*c,g*]thiocin (26e)

Conformation	$E_S$	$E_R$	$E_6$	$E_7$	$E_{12}$	$E_{NBI}$
$C_2$ chair $\rightleftharpoons$ $C_2$ chair*(34)	6.20	0.52	1.34	3.21	0.36	0.77
$C_2$ boat $\rightleftharpoons$ $C_2$ boat*(35)	12.70	1.58	4.35	3.60	0.49	2.67

\* All strain energies in  $\text{kcal mole}^{-1}$

but nonetheless it does seem likely that it will lie on the pseudorotational itinerary somewhere between the  $C_2$  chair (34) and  $C_1$  chair (36). Boat-like intermediates do not appear to be implicated in the  $C_2$  chair  $\rightleftharpoons$   $C_2$  chair\* (34) inversion process. The magnitudes ( $\Delta G^\ddagger = 9.8 - 13.7$  kcal mole $^{-1}$ ) of the free energies of activation for this inversion process for compounds 26b–26f are entirely in accord with a process involving torsion about single bonds and are in contrast with the much higher values ( $\Delta G^\ddagger = 15.5 - 16.3$  kcal mole $^{-1}$ ) for the olefinic '6,9,6' systems (25) where angle strain is an important contributor (Table 4) in the TS conformation (33).



$C_2$  chair (+---+---+)

$C_2$  chair\* (---+---+)

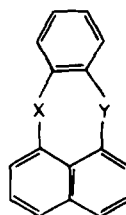
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The '6,10,6' systems (27) all exhibit sharp singlets for their dioxymethylene protons at low temperatures. The observation is consistent with conformations having  $C_2$  symmetry. For the *N*-benzyl derivative (27b), two AB systems, one for the C-12 and C-14 methylene protons and the other for the methylene protons of the benzyl group, are observed at low temperatures. Thus the ground state conformation must have  $C_2$  symmetry and the one that has been selected is the  $C_2$  chair (37). The magnitudes ( $\Delta G^\ddagger = 10.6 - 13.1$  kcal mole $^{-1}$ ) of the free energies of activation for ring inversion ( $C_2$  chair  $\rightleftharpoons$   $C_2$  chair\*) are once again entirely in accord with a pseudorotational process.

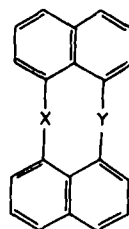
Strain energy calculations on '6,10,6' compounds (27) have not been carried out because of the problems introduced by potential  $p$ - $\pi$  conjugative interactions between the oxygen atoms and the aromatic rings, and also by potential 1,3-interactions<sup>34</sup> involving the two O atoms. However, the selection of the  $C_2$  chair (37) as the ground state conformation matches that selected by other investigators<sup>35</sup> for monocyclic *cis-cis*-cyclodeca-1,6-diene derivatives on the basis of conformational analysis.

#### The conformational behaviour of 1,8-bridged naphthalenes<sup>37</sup>

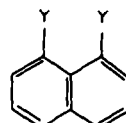
The stereochemistry and transannular reactions of 7,12-dihydropleiadenes (38) and of derivatives (39) of 7*H*,14*H*-dinaphtho[1,8-*b,c*:1',8'-*f,g*]cyclooctatetraene have attracted<sup>36</sup> a good deal of attention in recent years. Accordingly, we have turned our attention<sup>37</sup> to the incorporation of 1,8-disubstituted naphthalene units (40) as torsionally



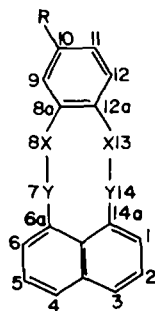
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41a: R = H; X = O; Y = CH<sub>2</sub>

41b: R = Me; X = O; Y = CH<sub>2</sub>

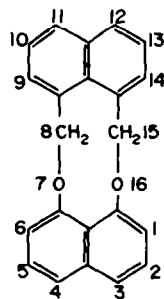
41c: R = H; X = S; Y = CH<sub>2</sub>

41d: R = Me; X = S; Y = CH<sub>2</sub>

41e: R = H; X = NMe; Y = CH<sub>2</sub>

41f: R = H; X = NTs; Y = CH<sub>2</sub>

42: R = H; X = CH<sub>2</sub>; Y = O



43

rigid groups into both 9-membered ring systems (41 and 42) and 10-membered ring systems (43).

In the heterocycles (41a, 41b, 41e, 41f and 42), we observe a *single* AB system at low temperatures for the ring methylene protons which coalesces to a sharp singlet at higher temperatures. This observation may be interpreted in terms of a ring inversion process involving conformations in which the methylene groups are related either by  $C_1$  symmetry [chair (C; 44) or boat (B; 45)] or by  $C_2$  symmetry [twist-boat (TB; 46)].

Conformational analysis indicates that the *peri*-interaction between the Y = CH<sub>2</sub> groups in 41a, 41b, 41e, and 41f is particularly large. This steric interaction is partially relieved in the TB conformation where the principal nonbonded interactions are

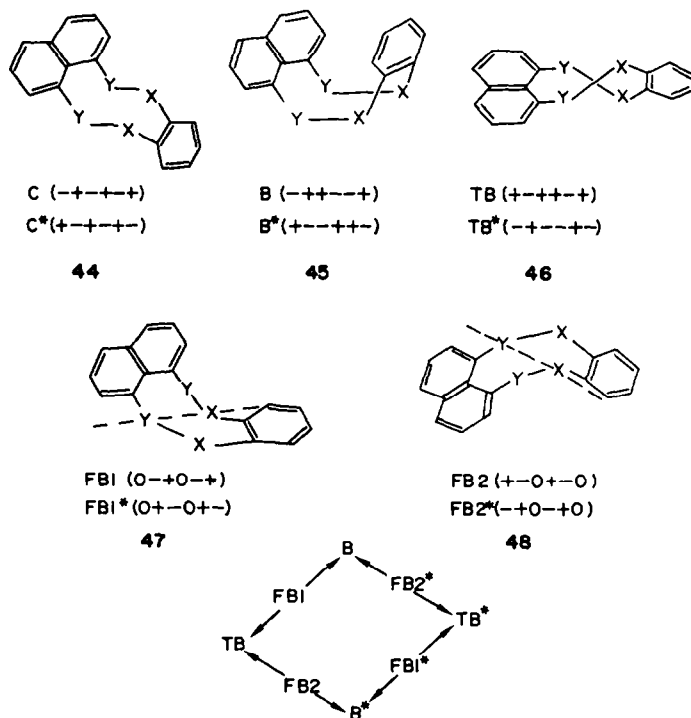


Fig 6. Conformational changes in compounds 41a, 41b, 41e, 41f, and 42. The notation for torsional angles (5) refers in turn to the 6a-7, 7-8, 8-8a, 12a-13, 13-14, and 14-14a bonds.

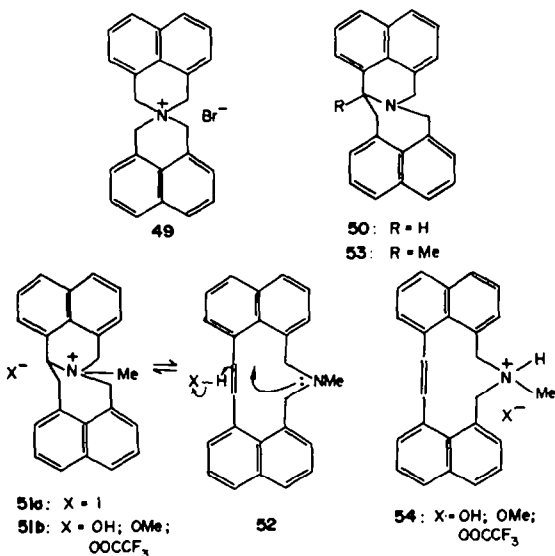
between the  $Y = CH_2$  groups and the heteroatoms ( $X = O, NR$ ). It seems likely therefore that the TB conformation (46) is the ground state and that ring inversion involves a  $TB \rightleftharpoons TB^*$  pseudorotational process (Fig 6). Three observations support this proposal: (i) The magnitudes (33 Hz for  $X = O$ , 87 Hz for  $X = NTs$ , 121 Hz for  $X = S$ , and 241 Hz for  $X = NMe$ ) of the chemical shift differences ( $\nu_A - \nu_B$ ) for the C-7 and C-14 methylene protons ( $CH_2H_B$ ) is found to depend significantly upon the nature of the ring heteroatoms. There are a number of examples<sup>36b,38</sup> where van der Waals interactions between heteroatoms and proximate protons lead to deshielding of the proton involved. The expectation<sup>39</sup> that the deshielding influence of heteroatoms will be related to their polarisabilities also appears to be fulfilled. (ii) When the heteroatoms in the compounds (41c and 41d) are both sulphur ( $X = S$ ) then transannular nonbonded interactions with the  $Y = CH_2$  groups destabilise the TB conformation sufficiently to permit the observation of approximately 20% of a second conformation at low temperatures. The minor conformation is presumably the C conformation (44). (iii) The fact that the free energies of activation for the  $TB \rightleftharpoons TB^*$  inversion process ( $\Delta G^\ddagger = 13.3$ – $15.9$  kcal mole<sup>-1</sup>) in the dithionins (41c and 41d) and diazonins (41f and 41g) are larger than those ( $\Delta G^\ddagger = 9.5$  kcal mole<sup>-1</sup>) for the dioxonins (41a and 41b) is consistent with the

pseudorotational process shown in Fig 6 where the FB conformations (47 and 48) correspond to the transition states. The main component of strain in these FB transition states arises from nonbonded interactions between  $Y = CH_2$  groups and the heteroatoms ( $X = O, S, NR$ ).

Similar considerations of chemical shift differences between the diastereotopic protons of the methylene groups, and the  $\Delta G^\ddagger$  values of 9.7 and 10.4 kcal mole<sup>-1</sup> for ring inversion in the dioxonin (42) and in the dioxecin (43), lead to similar conclusions; that is the conformational itineraries of compounds (42 and 43) also involve ring inversion ( $TB \rightleftharpoons TB^*$ ) between enantiomeric twist-boat conformations.

Strain energy calculations have not been performed on any of these systems (41, 42 and 43) because of the problems posed by the presence of heteroatoms adjacent to aromatic rings. However, the contrast between the conformational behaviour of these naphtho systems (41–43) and the '6,8,6' systems (2) is clearly evident, and no doubt results from the influence of the *peri*-interaction associated with 1,8-disubstituted naphthalenes. This unique geometry imposed by 1,8-disubstituted naphthalene residues has given rise to transannular interactions and reactions in numerous situations.<sup>36</sup> During a synthesis<sup>37</sup> of the 11-membered ring compound (52) from the spiro salt (49)<sup>40</sup> by a route (cf

Ref 41) involving a Stevens rearrangement and a Hofmann elimination, it was found that the enamine (52) undergoes transannular reactions in acidic, neutral (cf Ref 43a), and basic (cf Ref 43b) media to give quaternary ammonium salts (51).



monium salt 51b (X = OOCF<sub>3</sub>). All the evidence suggests that, in these reactions, the N-protonated species (54) is the product of kinetic control whereas the bicyclic ammonium salt (51), formed as a result of a "reverse Hofmann elimination" (52 → 51), is the thermodynamically more stable product. Relatively few transannular reactions between C=C double bonds and heteroatoms are known<sup>42</sup> and most require the presence of an acid catalyst (for a discussion of some exceptions, see Ref 43). In the present case, the propensity for the enamine (52) to undergo a transannular reaction is most likely explained by the favourable transition state developing out of the boat conformation (55). To our knowledge this is the first example of this particular class of transannular reactions in bis-1,8-dinaphtho systems.

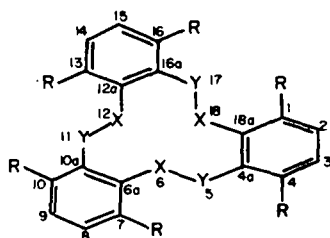
Treatment of the spiro salt (49) with phenyl lithium afforded the bicyclic amine (50) which was converted to the methiodide (51a). All attempts at direct pyrolysis of the derived hydroxide 51b (X = OH) were unsuccessful and starting material was always recovered unchanged. However, when the hydroxide 51b (X = OH) was heated under reflux with dry toluene in a Dean-Stark apparatus, elimination proceeded smoothly giving the crystalline enamine (52) as the major product and the Stevens rearrangement product (53) as a minor constituent. The enamine (52) was shown to be conformationally stable on the NMR time scale since the AB system for the ring methylene protons remained sharp up to +160° in nitrobenzene solution.

The enamine (52) has been shown to undergo transannular reactions in three different experiments: (i) Treatment of an ethanolic solution of compound 52 with hydroiodic acid for 2 h gave the methiodide (51a) in 72% yield. When compound 52 was stirred, either (ii) in aqueous methanol at room temperature for 48h, or (iii) in aqueous methanol adjusted to pH 10 (NH<sub>3</sub>) under the same conditions, NMR spectroscopy of the product in trifluoroacetic acid indicated the presence of the transannular product (51b) and the N-protonated species (54) in the approximate ratio of 1:2. Previously, it had been established that a solution of the enamine (52) in dimethylsulphoxide-*d*<sub>6</sub> contains *only* the N-protonated species 54 (X = OOCF<sub>3</sub>) on addition of trifluoroacetic acid and *none* of the bicyclic am-

*The conformational behaviour of hexahydrotri-benzo[a,e,i]cyclododecaene (56) and related systems*

In addition to discussing the conformational behaviour of 5,6,11,12-tetrahydrodibenzo[a,e]cyclooctene (4) in their pioneering paper in 1945, Baker *et al.*<sup>1</sup> also considered some of the possible conformations that 5,6,11,12,17,18-hexahydrotribenzo[a,e,i]cyclododecaene (56) could adopt. Recently, we examined<sup>44</sup> the temperature dependence of the NMR spectrum of compound 56 in carbon disulphide solution and found that the sharp singlet for the -CH<sub>2</sub>-CH<sub>2</sub>- protons at room temperature became a broad *unsymmetrical* multiplet at -80° indicating the presence of a conformation devoid of 3-fold symmetry. In order to examine this problem in more detail we prepared<sup>45</sup> the 1,4,7,10,13,16-hexamethyl derivative (57). The NMR spectrum of this compound in deuteriochloroform solution showed temperature dependence. Three singlets for the Me groups at room temperature coalesced to a sharp singlet at +80°.

Examination of molecular models suggests that the 12-membered ring of compounds 56 and 57 can adopt two conformations in the ground state, one with C<sub>2</sub> symmetry (60), and the other with D<sub>3</sub> symmetry (61). These two conformations are analogous to the helical (H) (60) and propeller (P) (61) conformations of the trisallycylides (3).<sup>6</sup> The interconversion between the H and P conformations and their enantiomers H\* and P\* is specified



- 56: R = H; X = Y = CH<sub>2</sub>  
 57: R = Me; X = Y = CH<sub>2</sub>  
 58: R = H; X = CH<sub>2</sub>; Y = S  
 59: R = H; X = CO; Y = NMe

in Fig 7. Strain energy calculations have been performed on the ground state conformations (60 and 61) and on probable transition states for  $P \rightleftharpoons H$  ( $P^* \rightleftharpoons H^*$ ) interconversion and  $H \rightleftharpoons H^*$  inversion. The transition state geometries in the TS1 (62) and TS2 (63) conformations were defined by holding a bis-methylene unit in the plane of one of the aromatic rings; for example C-4a, C-5, C-6, C-6a, C-10a, C-11 were 'held' coplanar. The results recorded in Table 6 for the hydrocarbon (57) are in good agreement with the conclusion reached on the basis of NMR line shape analysis which indicated that any contribution at equilibrium (Table 7) from the propeller ( $D_3$ ) conformation (61) must amount to less than 0.8%. The strain energy calculations predict that the Helix ( $C_2$ ) conformation (60) is more stable ( $\Delta G_{\text{calc}} = ca\ 1.5\ \text{kcal mole}^{-1}$ ) than the Propeller ( $D_3$ ) conformation (61). This situation contrasts (Table 7) with that exhibited by the trisallyclides (3), for which in all cases so far examined<sup>6</sup>, both helical ( $C_2$ ) and propeller ( $C_3$ ) conformations are present with the more symmetrical propeller ( $C_3$ ) conformation always being preferred. Finally, there is excellent agreement between the  $\Delta G_{\text{obs}}^\ddagger$  of  $17.1\ \text{kcal mole}^{-1}$  and the  $\Delta G_{\text{calc}}^\ddagger$  of  $16.3\ \text{kcal mole}^{-1}$  (Table 6) for the  $H \rightleftharpoons H^*$  inversion process of the hydrocarbon (57).

Strain energy calculations have also been performed<sup>6</sup> (Table 6) on the parent hydrocarbon (56). They indicate that, in common with the hexamethyl derivative (57), the helical ( $C_2$ ) conformation (60) is more stable than the propeller ( $D_3$ )

conformation (61). They also predict that the barrier to  $H \rightleftharpoons H^*$  inversion is less than half that found in the hexamethyl derivative (57). At the moment we lack quantitative experimental information on the parent hydrocarbon (56). However, the temper-

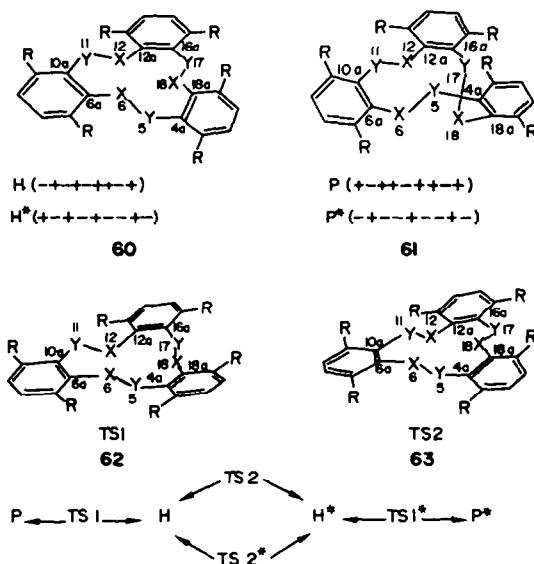


Fig 7. Conformational changes in compounds 3, 56-59. The notation (5) for torsional angles refers in turn to the 4a-5, 5-6, 6-6a, 10a-11, 11-12, 12-12a, 16a-17, 17-18, and 18-18a bonds.

Table 6. Strain energies<sup>a</sup> of selected conformations of 5,6,11,12,17,18-hexahydrotribenzo[*a,e,i*]-cyclododecaene (56) and its hexamethyl derivative (57)

Conformation	Hydrocarbon (56)						Hydrocarbon (57)					
	$E_S$	$E_R$	$E_o$	$E_e$	$E_\Delta$	$E_{NBI}$	$E_S$	$E_R$	$E_o$	$E_e$	$E_\Delta$	$E_{NBI}$
$P \rightleftharpoons P^*$ (61)	5.87 <sup>b</sup>	0.23	3.12	0.84	0.47	1.21	4.96 <sup>b</sup>	0.31	2.47	1.53	0.65	0.00
$H \rightleftharpoons H^*$ (60)	2.96 <sup>b</sup>	0.17	1.58	0.56	0.20	0.45	4.11 <sup>bc</sup>	0.35	2.71	0.76	0.24	0.05
TS1 $\rightleftharpoons$ TS1* (62)	15.79	0.50	11.21	1.18	0.20	2.70	21.85	0.96	12.99	1.87	0.98	5.05
TS2 $\rightleftharpoons$ TS2* (63)	9.74	0.24	6.71	1.34	0.59	0.86	20.79 <sup>c</sup>	0.87	15.29	1.43	0.76	2.44

<sup>a</sup> All strain energies in kcal mole<sup>-1</sup>.

<sup>b</sup> The Helix conformation is also favoured by entropy. On the basis of symmetry considerations alone, the Helix conformation, which has a symmetry number of 2, will be  $R \ln 3\ \text{cal K}^{-1}\ \text{mole}^{-1}$  higher in entropy than the Propeller conformation which has a symmetry number of 6.

<sup>c</sup> If the difference in strain energies between the Helix conformation and the TS2 (TS2\*) transition state for  $H \rightleftharpoons H^*$  inversion is equated with  $\Delta H^\ddagger$  then an appropriate estimate for  $\Delta G_{\text{calc}}^\ddagger$  of  $16.3\ \text{kcal mole}^{-1}$  follows from recognising that the transition state is favoured on entropy grounds by  $R \ln 2\ \text{cal K}^{-1}\ \text{mole}^{-1}$  (i.e. the CH<sub>2</sub>CH<sub>2</sub> unit can rotate in two equivalent ways).

Table 7. Relative conformer populations in 12-membered ring compounds

Compound	Propeller %	Helix %
Hydrocarbon (57) (CDCl <sub>3</sub> soln. at 20°)	< 1	> 99
Trisulphide (58) (CS <sub>2</sub> soln. at -106°)	< 1	> 99
Tri- <i>o</i> -thymotide (3c) (C <sub>2</sub> HCl <sub>3</sub> soln. at 68°)	86	14
Tri- <i>o</i> -thymotide (3c) (C <sub>2</sub> HCl <sub>3</sub> soln. at 90°)	80	20
Tri- <i>o</i> -carvacrotide (3b) (C <sub>2</sub> H <sub>5</sub> N soln. at 20°)	64	36
Tri- <i>o</i> -carvacrotide (3b) (C <sub>2</sub> H <sub>5</sub> N soln. at 90°)	58	42
Tri-3,6-dimethyl-salicylide (3a) (CDCl <sub>3</sub> soln. at -10°)	67	33
N,N,N-Trimethyl-trianthranilide (59) (CDCl <sub>3</sub> soln. at 20°)	2	98

ature dependence of the NMR spectrum in the range +20° to -80° indicates a free energy of activation for H⇌H\* inversion of less than 10 kcal mole<sup>-1</sup>. Clearly, the replacement of *ortho*-Me substituents by H atoms leads to a significantly more mobile 12-membered ring. This is certainly the case with the cyclic trisulphide 6,12,18-trihydrotribenzo[*b, f, j*][1, 5, 9]trithiacyclododecin (58).<sup>47</sup> The NMR spectrum of this heterocyclic compound (58) in carbon disulphide showed temperature dependence. Three AB systems for the ring methylene protons at -106° were identified by homonuclear INDOR spectroscopy. The AB systems coalesced to a sharp singlet at -36°. The ground state conformation is therefore characterised by C<sub>1</sub> symmetry and has been designated as a Helix (60). The free energy of activation for H⇌H\* inversion was found to be 9.3 kcal mole<sup>-1</sup> and is therefore very much smaller than the barrier ( $\Delta G_{\text{obs}}^{\ddagger} = 17.1$  kcal mole<sup>-1</sup>) to H⇌H\* inversion in the hydrocarbon (57) with six *ortho*-Me substituents.

*ortho*-Alkyl substituents also influence the activation parameters (Table 8) for the conformational changes in the trisalicylides (3). For tri-*o*-thymotide (3c), the kinetics of conformational change have

been examined by NMR line-shape methods and by measurement of the rate of racemisation of optically active tri-*o*-thymotide. The agreement between the activation parameters obtained by both methods is good (Table 8). The CD of tri-*o*-thymotide (3c) in ether solution at -78° or in a potassium chloride disc at 20° shows<sup>6</sup> that the (+)-isomer has the absolute configuration associated with the *M*-propeller conformation (64). Finally, the *trans*-ester linkages in tri-*o*-thymotide (3c) have been established<sup>48</sup> by an X-ray crystal structure investigation (Fig 8).

Recently, we have prepared<sup>49</sup> N,N,N-trimethyl-trianthranilide (59) and have shown that its crystals are derived from the Helix conformation (60). In

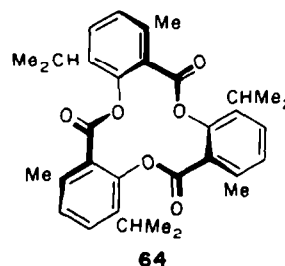


Table 8. Activation parameters for conformational changes in 12-membered ring compounds

Compound	Solvent	Process	$\Delta G^{\ddagger}$ (kcal mole)
Hydrocarbon (57)	CDCl <sub>3</sub>	H⇌H*	17.1 ± 0.3
Trisulphide (58)		H⇌H*	9.3 ± 0.2
Tri-3,6-dimethyl-salicylide (3a)	CDCl <sub>3</sub>	Propeller → Helix	18.0 ± 0.5
		H⇌H*	14.3 ± 0.5
Tri- <i>o</i> -carvacrotide (3b)	C <sub>2</sub> D <sub>5</sub> N	Propeller → Helix	20.6 ± 0.2
		Helix → Propeller	20.3 ± 0.2
		H⇌H*	17.6 ± 0.2
Tri- <i>o</i> -thymotide (3c)	CDCl <sub>3</sub>	P⇌P*	20.9*
		Propeller → Helix	20.1 ± 0.3
		Helix → Propeller	19.5 ± 0.3
		P⇌P*	20.5 ± 0.3
N,N,N-Trimethyl-trianthranilide (59)	PhNO <sub>2</sub>	Propeller → Helix	21.6 ± 0.5
		H⇌H*	24.4 ± 0.5

\* Determined by recalculation from the published figures [A. C. D. Newman and H. M. Powell, *J. Chem. Soc.* 3747 (1952)] provided by polarimetric examination of the racemisation of tri-*o*-thymotide-benzene clathrate in chloroform solution.

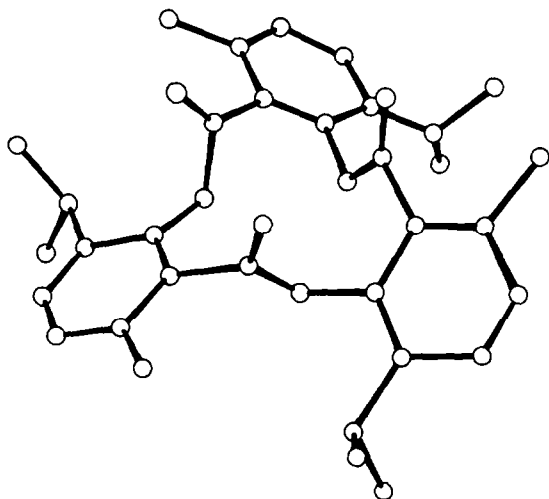
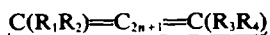


Fig 8. The structure of tri-*o*-thymotide (3c) in the solid state.<sup>48</sup>

solution this Helix conformation is in equilibrium with a small amount (*ca* 2%) of the Propeller conformation (61). This corresponds to a difference in free energy of *ca* 2.6 kcal mole<sup>-1</sup> between the two conformations and indicates along with the activation parameters (Table 8) for conformational change that the transition states for P $\rightleftharpoons$ H interconversion (TS1) ( $\Delta G_{\text{Propeller} \rightarrow \text{Helix}}^\ddagger = 21.6 \pm 0.5$  kcal mole<sup>-1</sup>) and for H $\rightleftharpoons$ H\* inversion (TS2) ( $\Delta G_{\text{H} \rightarrow \text{H}^*}^\ddagger = 24.4 \pm 0.5$  kcal mole<sup>-1</sup>) are very similar in their energetic demands.

#### CONCLUDING REMARKS

It is appropriate to include in this paper a few remarks on the relation between the results now reported on the conformational behaviour of medium-sized ring systems and the 1874 publications of van't Hoff<sup>50</sup> and LeBel.<sup>51</sup> van't Hoff predicted<sup>52</sup> the existence of dissymmetric molecules which did not contain centres of asymmetry associated with single atoms. His exact form of words and the formula he used<sup>52</sup> deserve repetition: "*le deuxième cas d'activité optique; il pourrait se traduire par la formule:*



*R*<sub>1</sub> doit être différent de *R*<sub>2</sub>, *R*<sub>3</sub> de *R*<sub>4</sub>, sans que toutefois la différence de *R*<sub>1</sub> et *R*<sub>3</sub> ou *R*<sub>4</sub> soit nécessaire". Clearly this prediction included substituted allenes (65) and on the basis of the origin of this quotation,<sup>52</sup> it is not appropriate to suggest<sup>53</sup> that this proposal should be attributed to F. Herrmann.<sup>54†</sup>

The resolution in 1909 of 4-

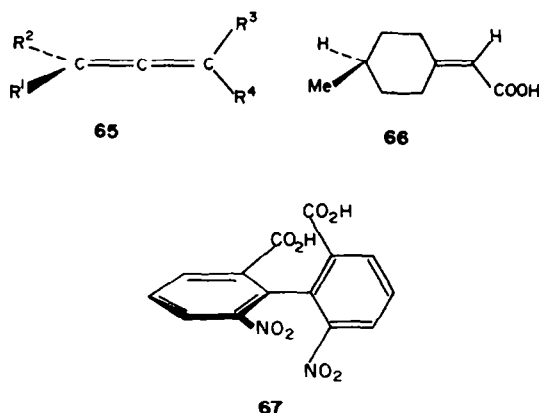


Fig 9. Dissymmetric molecules which do not contain centres of asymmetry associated with single atoms.

methylcyclohexylidene-acetic acid (66)<sup>55</sup> was the first example of molecular dissymmetry of this type (Fig 9). However, it was not until 1935 that the resolution of allenes (65) was achieved.<sup>56</sup>

In 1922, Christie and Kenner,<sup>57</sup> working in the University of Sheffield, obtained the enantiomeric forms of 2,2'-dinitrobiphenyl-6,6'-dicarboxylic acid (67). The importance of this contribution has been assessed by D. H. R. Barton in his Nobel Lecture "The Principles of Conformational Analysis".<sup>58</sup> He noted that the resolution of 2,2'-dinitrobiphenyl-6,6'-dicarboxylic acid (67) was not only an example of molecular dissymmetry which was not associated with particular single atoms, but it was also the first experimental demonstration that rotation about formal single bonds could be restricted. This was an important development in relation to van't Hoff's opinion<sup>50,52,59</sup> that rotation about double bonds was "restricted" whereas rotation about single bonds was "free".

The determination of the absolute configuration<sup>60</sup> of allenes (65),<sup>61</sup> 4-methylcyclohexylideneacetic acid (66),<sup>62</sup> and biphenyls (e.g. 67)<sup>63</sup> followed much later.

Although the conformations of the compounds studied in our investigations are often chiral,<sup>8c,64,65</sup> the chirality is not associated with centres, axes, or planes of chirality;<sup>53</sup> it is helical in origin in the manner that has been elegantly analysed by Cahn, Ingold, and Prelog.<sup>64</sup> This kind of chirality echoes the 1860 commentary by Pasteur<sup>56</sup> which included the proposal that molecular dissymmetry could be associated with helicity.

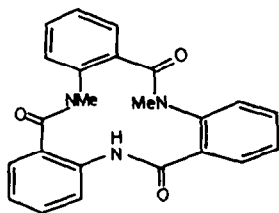
Our investigations of the conformational behaviour of '6,8,6', '6,9,6', and '6,10,6' systems, 1,8-bridged naphthalenes and 12-membered ring compounds were made possible using the temperature dependent NMR method<sup>7</sup> because the ground state conformations contained protons or groups showing diastereotopic relationships<sup>8c,67,68</sup> which were

†We thank Professor V. Prelog for consultation on this point.



exchanged by conformational changes. The results have provided particularly instructive examples of the efficiency of this method, which is not only informative when the site exchange process involves recognisably diastereotopic groups, but also when homotopic or enantiotopic groups are involved. The determination of the temperature dependence of the site exchange rates leads to activation parameters which can be directly compared with the results of molecular mechanics calculations.

What of the future? In our view the correlation which is now beginning to emerge between activation parameters for conformational changes involving inversion and interconversion which are calculated and experimentally determined is remarkably satisfactory, encouraging and satisfying. This augurs well for the continued development of this general approach in conformational analysis well beyond the confines of medium-sized cyclic systems. We share the optimism of Schleyer<sup>8a</sup> and Allinger<sup>13</sup> regarding the computational method as a further experimental technique to be developed and applied by organic chemists. Computational methods can clearly be used to determine the conformational characteristics of molecules. This approach enables preferred ground state conformations to be selected and decisions to be taken regarding the relative merits of transition state conformations. This is important: the approach can and will be used with greater accuracy than is possible on the basis of opinions formed only by the inspection of molecular models. In time the caution which is sometimes exhibited with respect to such computational methods will be replaced by confidence.



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Finally, mention must be made of delightful but unpredictable dividends associated with this type of investigation. Examples include (i) the spontaneous resolution of tri-*o*-thymotide (3c) and its use as a resolving agent,<sup>6</sup> and (ii) the isolation and characterisation of two conformational isomers, m.p. 182–184° and m.p. 251–254°, of *N,N*-dimethyl-tri-anthranilide (69).<sup>49</sup>

In a somewhat light-hearted vein it is perhaps appropriate to conclude this review by a direct quota-

tion from Louis Pasteur's Second Lecture to the Chemical Society of Paris given in 1860:<sup>66</sup>

"This general conclusion from the above-mentioned investigations throws a new light on our ideas of molecular mechanics."

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