Stabilizing the Boat Conformation of Cyclohexane Rings

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Abstract: In calculating the energetics for various conformers of the **A**, **B**, and **C** series of hopanoid hydrocarbons present in mature oil reservoirs, we find that the **B** series prefers the boat conformation (by 1.3–2.5 kcal/mol) for the D cyclohexane ring (see Figures 1 and 2). We analyze the structural elements responsible for stabilizing this boat conformation, identify the key features, and illustrate how one might stabilize boat conformations of other systems.

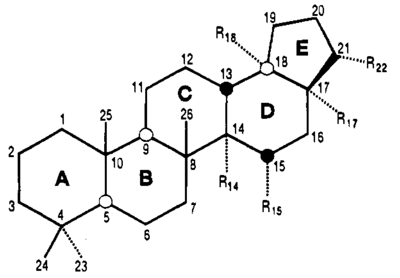
Cyclohexane rings, **1**, are ubiquitous in organic systems. In all known biological systems these rings have the chain conformation in which the ligands at each of the six CC bonds are staggered.[1] The boat conformation leads to eclipsed bonds with destabilizing H–H contacts, which are partially relaxed by distorting slightly into a twist-boat conformation. For simplicity we refer to this twist-boat optimum conformation as boat form or simply "boat". This leads to an energy 5.2 kcal/mol higher than the chair form.[2] In the process of predicting structures for rearranged hopanoid hydrocarbons prevalent in mature oil reservoirs,[3] we discovered one class (the **B** series or 17α(*H*)-diahopanes of Figure 1) that strongly *prefer* the boat conformation over the chair. The stability of boat over chair is predicted to be 2.57 kcal/mol for the **B3** molecule (17α(*H*)-15α-methyl-27-norhopane), a preference verified by X-ray diffraction. We analyze here the origins of this conformational preference in order to indicate how one might stabilize the boat conformation over chair by use of appropriate organic substitutions.

We use the MM3 force field[2b] (optimized to describe conformations of hydrocarbons) to predict the conformational preferences for the various components of **B3**. The results are summarized in Table 1. The notation in Table 1 and Figure 3 is as follows: (i) $\Delta = (E_{\text{boat}} - E_{\text{chair}})$, all energies in kcal/mol; (ii) the atoms are numbered to correspond with the standard numbering in **B3**; (iii) α is the target ring, which prefers the boat conformation in **B3**; (iv) 5 denotes a five-membered ring fused to α using the axial H of C-17 and the equatorial H of C-18; (v) *M* denotes a methyl group at C-15 of the α ring; and (vi) γ denotes a cyclohexane ring fused to the equatorial H's of C-8 and C-9 in the β ring.

Table 1. Substitutional Effects (kcal/mol) on the Boat–Chair Energy Difference, Evaluated using MM3

	structure	$E_b - E_c$, Δ	incremental effects			
			add 5	add *M*	add γ	add *M*γ
1	α	5.76				
2	αβ	6.45				
3	5αβ	3.17	−3.28[a]			
5	αβ*M*	6.71		+0.26		
7	αβγ	5.89			−0.56	
8	αβγ*M*	1.45		−4.44	−5.26	−5.00[b]
4	5αβ*M*	3.24	−3.47	+0.07		
9	5αβγ	2.48	−3.41		−0.69	
6	5αβγ*M*	−3.27	−4.72[c]	−5.75	−6.51	−6.44[c]

[a] Thus $\delta_5 = -3.3$. [b] Thus $\delta_{\gamma M} = -5.0$. [c] Thus $\delta_{5,\gamma M} = -1.4$.



Series	A1	A2	A3	B1	B2	B3	C1	C2	C3
Substituent R_{22}	H	Et	iPr	H	Et	iPr	H	Et	iPr
(The following substituents are common to all members of each series)									
R_{14}	Me_{27}			H			Me_{27}		
R_{15}	H			Me_{27}			H		
R_{17}	Me_{28}			H			H		
R_{18}	H			Me_{28}			Me_{28}		

Figure 1. Hopane structures. The **A**, **B**, or **C** is combined with substituents 1, 2, 3. Thus **B3** has R_{22} = iPr.

The essential elements in destabilizing the chair form of α are the following: (i) The first essential element is the presence of the five-membered ring. For chair it provides destabilizing interactions with the α and β rings from above ($\delta_5 = \Delta_{5\alpha\beta} -$

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Table 2. The Boat–Chair Energy Difference (kcal/mol) for Various Substituents (R) on the **A**, **B**, and **C** Series in Figure 2 (Evaluated Using MM3)[a]

substitution	A	B	C
1 (H)	+3.77	−1.26	+2.85
2 (C_2H_5)	+3.02	−1.98	+2.72
3 (iC_3H_7)	+3.19	−2.47	+0.53
ΔH_f(H)	−77.83	−81.77	−76.16

[a] The heat of formation is shown for R = H using the most stable conformation (ring D in the chair conformation of **A1** and **C1** and the boat conformation of **B1**).

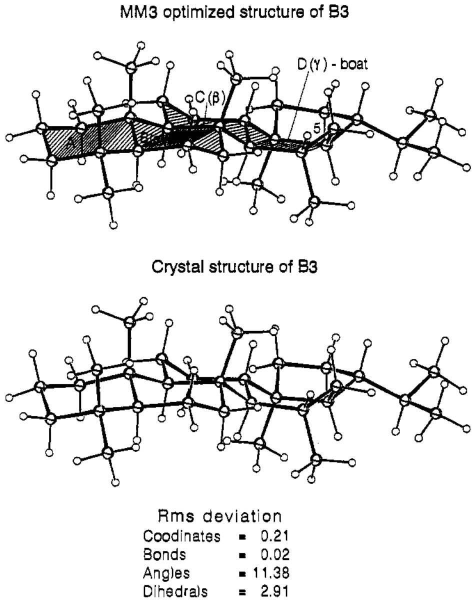

Figure 2. Perspective views of the crystal structure and the calculated MM3 structure of the boat form of **B3**.

$\Delta_{\alpha\beta} = -3.3$). This is dominated by H-12::H-19 = 2.15 Å and H-15::H-21 = 2.26 Å for chair, much shorter than the normal contact distance of ~2.4 Å. (ii) The second element is the simultaneous presence of γ and *M*. This leads to destabilizing interactions on the bottom ($\delta_{\gamma M} = \Delta_{\alpha\beta\gamma M} - \Delta_{\alpha\beta} = -5.0$). This is dominated by H-7::H-27 which is 1.86 Å in chair and 2.26 Å in boat. Adding γ or *M* separately leads to much smaller effects ($\delta_\gamma = \Delta_{\alpha\beta\gamma} - \Delta_{\alpha\beta} = -0.6$ and $\delta_M = \Delta_{\alpha\beta M} - \Delta_{\alpha\beta} = +0.3$). (iii) The third element is the interaction of the 5 and γ*M* substitutions [$\delta_{5,\gamma M} = \delta_{5\gamma M} - \delta_5 - \delta_{\gamma M} = (\Delta_{5\alpha\beta\gamma M} - \Delta_{\alpha\beta}) - (\Delta_{5\alpha\beta} - \Delta_{\alpha\beta}) - (\Delta_{\alpha\beta\gamma M} - \Delta_{\alpha\beta}) = -1.4$]. With only one of 5 or γ*M* the destabilizing HH interactions can be accommodated by distorting the molecule. However, with destabilizing interactions on both faces of the ring, the unfavorable HH contacts cannot be relaxed, leading to a further decrease in Δ.

Thus for the chair form of **6** H-12::H-19 decreases to 2.10 Å from 2.15 Å in **3**. The total differential effect from (i), (ii), and (iii) is $\delta_{5+\gamma M} = -3.3 - 5.0 - 1.4 = -9.7$. Combining this with $\Delta_{\alpha\beta} = 6.45$ leads to $\Delta_{5\alpha\beta\gamma M} = -3.3$.

The structure **6** = $5_{\alpha\beta\gamma M}$ corresponds to the *BCDE-M*$_{27}$ portion of **B1** (Figure 1). Adding the other methyl substituents of the BCDE rings (M_{26}, M_{28}, and axial M_{25} to C-8, C-18, and C-10) converts **6** to **10** reducing the preference for boat from $\Delta_6 = -3.27$ to $\Delta = -0.95$. This corresponds to the preference of **B1** for the boat D ring since it is close to the observed value of $\Delta_{B1} = -1.26$. **B2** and **B3** have bulkier substituents at C_{21} and have slightly higher preference for the boat form, $\Delta_{B2} = -1.98$ and $\Delta_{B3} = -2.47$ kcal/mol (Table 2). Of the **B** series, an X-ray study[4] has been reported only for **B3**. Unexpectedly the published figure[4] shows the *chair* form for ring D. In order to determine where our analysis had gone wrong, we obtained the actual coordinates for the X-ray study. In fact we found excellent agreement of the X-ray structure with the predicted structure (rms = 0.12 Å for coordinates and 2.91° for dihedrals) (Figure 2). In particular, the D ring is boat! (The picture in ref 4 was incorrectly drawn assuming chair rather than boat for the D ring.)

Neither the **A** or the **C** series have M_{27}. From Table 1 this should stabilize chair by 2.48 + 3.27 = 5.75, suggesting that Δ = −1.26 + 5.75 = 4.5 for **A1** and **C1**. Indeed we calculate $\Delta_{A1} = 3.8$ and $\Delta_{C1} = 2.9$. This chair form of the D ring for **A1** is confirmed by X-ray studies[5] and the chair structure for **A2** is confirmed by NMR studies.[4]

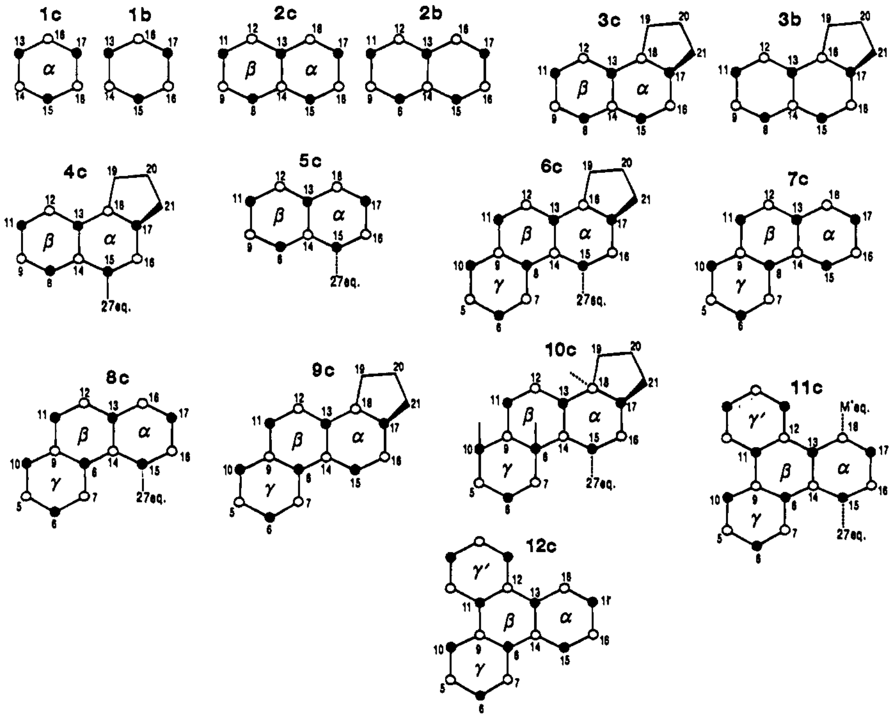

Figure 3. Structures for model systems. The configuration of the α ring is indicated by **c** for the chair form and **b** for the boat form.

These results suggest that adding γ' and M' to $\alpha\beta\gamma M$ to form **11** = $\alpha\beta(\gamma M)(\gamma' M')$ would strongly prefer the boat conformation. Assuming no interaction between γ and γ' and M and M', we would expect $\Delta_{11} \approx \Delta_8 - 5.0 = -3.55$, in reasonable agreement with MM3 calculations, which lead to $\Delta_{11} = -1.89$. Eliminating M and M' from **11** leads to **12** = $\alpha\beta\gamma\gamma'$ with $\Delta_{12} = 5.03$, indicating that M and M' each stabilize boat by ~3.5. This example illustrates how the ideas of this paper can be used to design or predict a new structure stabilizing the boat form of a cyclohexane ring.

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