JOURNAL OF PHYSICAL ORGANIC CHEMISTRY, VOL. 11, 781–786 (1998)

Conformational analysis of substituted 5,6,7,8-tetrahydrodibenzo[*a,c*]cyclo-octene: comparison of ^{1}H NMR, molecular mechanics and semiempirical methods

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Received 1 October 1996; revised 12 January 1998; accepted 12 January 1998

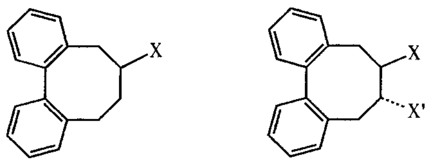
ABSTRACT: The 6-Mono- and *trans*-6,7-di-substituted derivatives of 5,6,7,8-tetrahydrodibenzo[*a,c*]cyclo-octene exist in solution in two different conformations. The experimental ΔG^o values obtained from ^{1}H NMR spectra are compared with the $\Delta E_{\mathrm{steric}}$ and ΔG values calculated by molecular mechanics and semiempirical quantum mechanics methods respectively. The experimental ΔG^o values are reproduced better by the $\Delta E_{\mathrm{steric}}$ values. The semiempirical methods predict the order of stability of the conformers correctly except for two cases in the PM3 and AM1 methods, but the estimated values are far from the experimental ones. The standard deviation between the experimental ΔG^o values and those calculated by semiempirical methods is less for AM1 and MNDO and greater for PM3 and MINDO/3. The conformational space of the flexible side chains in monoacetoxy **1d**, monohydroxy **1e**, *trans*-diacid **2d**, *trans*-dimethyl ester **2e** and *trans*-bis-hydroxymethyl **2f** searched by molecular mechanics is not reproduced completely by semiempirical methods. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: eight membered rings; conformational analysis; molecular mechanics; semiempirical methods

INTRODUCTION

Conformational analysis is performed by experimental as well as computational methods. Experimental determinations of conformations are of interest not only in themselves but also because they provide a check on conclusions drawn from computational methods. On the other hand, computational methods are important as many experimental data can be analysed and explained by such techniques. Most experimental information comes from X-ray diffraction studies of crystalline compounds and NMR measurements in solution. NMR is a very valuable tool for conformational studies especially as the solution rather than the solid state is investigated and thus lattice forces can be excluded. Among the computational methods, molecular mechanics and semiempirical quantum mechanics methods are the most popular and widely used.

Cyclo-octa-1,3-diene and its dibenzo analogue 5,6,7,8-tetrahydrodibenzo[*a,c*]cyclo-octene (**1a**, Scheme 1) have been studied by ^{1}H and ^{13}C NMR spectroscopy and by force field calculation.[1,2] Two types of minimum energy conformation are possible, the lower one being described as twisted boat–chair (TBC) and the higher one as twisted boat (TB). In cyclo-octa-1,3-diene the TB conformation is estimated to be only 2.1 kJ mol^{-1} higher in energy than the TBC one.[2] The ^{1}H and ^{13}C NMR spectra of cyclo-octa-1,3-diene are temperature-dependent, showing the TB and TBC conformations in almost the same ratio at -175 °C. The ^{1}H and ^{13}C NMR spectra of **1a** show no exchange broadening down to -80 °C. At lower temperatures this compound crystallizes in the NMR tube, so dynamic NMR measurements cannot be followed. The difference between the TB and TBC conformations in **1a** is estimated to be 11.8 kJ mol^{-1}, the latter being lower in steric energy.[1] The TB conformation should not be present to more than a few per cent, if at all. This conclusion was established by analysing the ^{1}H NMR



1 a; X= H
b; X= Cl
c; X= Br
d; X= OAc
e; X= OH

2 a; X= Me
b; X= Cl
c; X= Br
d; X= CO_2H
e; X= CO_2Me
f; X= CH_2OH

Scheme 1

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Contract/grant sponsor: Research Council of Tehran University.

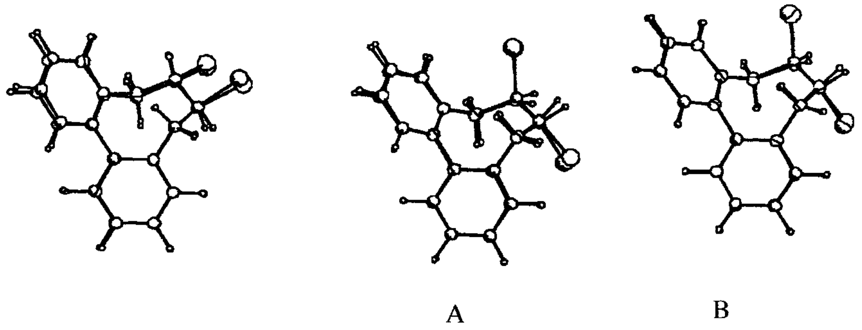


Figure 1. Superimposition of X-ray structures and calculated structures (MMP2-87) of the two conformational diastereomers of **2c**

spectra of 6-mono- and *trans*-6,7-di-substituted derivatives of **1a**.[1]

The ^{1}H and ^{13}C NMR spectra of 6-mono- and *trans*-6,7-di-substituted derivatives of **1a** show an equilibrium between the two conformations in solution. Therefore they are a unique set for conformational analysis and it is desirable to check the scope and limitations of computational methods applied to these compounds.

RESULTS AND DISCUSSION

The *trans*-6,7-dibromo derivative **2c** was crystallized to determine the preferred conformation in the solid state. This compound crystallized in two different crystal shapes, namely coarse and plate. These crystals were shown by X-ray crystallography to have the bromine atoms in the equatorial–equatorial (*e,e*) and axial–axial (*a,a*) positions respectively, both adopting the TBC conformation.[3] In the crystal structure of the coarse crystals, only one type of molecule was found which is superimposable on the calculated structure with a mean deviation of 0.11 Å (Fig. 1). Two independent molecules A and B were found in the plate crystals. Both have very similar structures that are best fitted with a root mean square distance between the non-hydrogen atoms of 0.11 Å. The mean deviation in the best fit of the calculated *a,a* form is 0.26 Å for the A molecule and 0.06 Å for the B molecule (Fig. 1). The coarse and plate crystals, which were shown to be the *e,e* and *a,a* forms respectively, were dissolved in $CDCl_3$ at low temperature and the ^{1}H NMR spectra were recorded immediately. The 1H NMR spectra of the coarse and plate crystals show major and minor resonances respectively compared with the ^{1}H NMR spectrum of the equilibrated sample (Fig. 2). Analysis of the coupling constant of the bridge protons of the two forms of the dibromo compound supports the assignment of the major and minor forms as *e,e* and *a,a* respectively in the TBC conformation.[1,3]

The ^{1}H and ^{13}C NMR spectra of other 6-mono- and *trans*-6,7-di-substituted derivatives of **1a** also show resonances of the two forms in different ratios. Careful analysis of the 5-H and 6-H resonances of **1b** and the 5-H and 6-H (or 7-H) resonances of **2b** (Table 1, Fig. 3) indicates that the TBC conformation is predominant and that the TB conformation should not be present to more than a few per cent, if at all. Assignment of the major form as *e* for the 6-mono- and *e,e* for the *trans*-di-substituted compounds in the TBC conformation is therefore straightforward (Table 2).[1]

The ratio of the two forms could be derived directly from the ^{1}H NMR spectra, whereby the equilibrium constant and ΔG^{o} values could be estimated (Table 3). The *e–a* and *e,e–a,a* equilibrium constants for compounds **1b, 1c** and **2a, 2b, 2c** are almost insensitive to

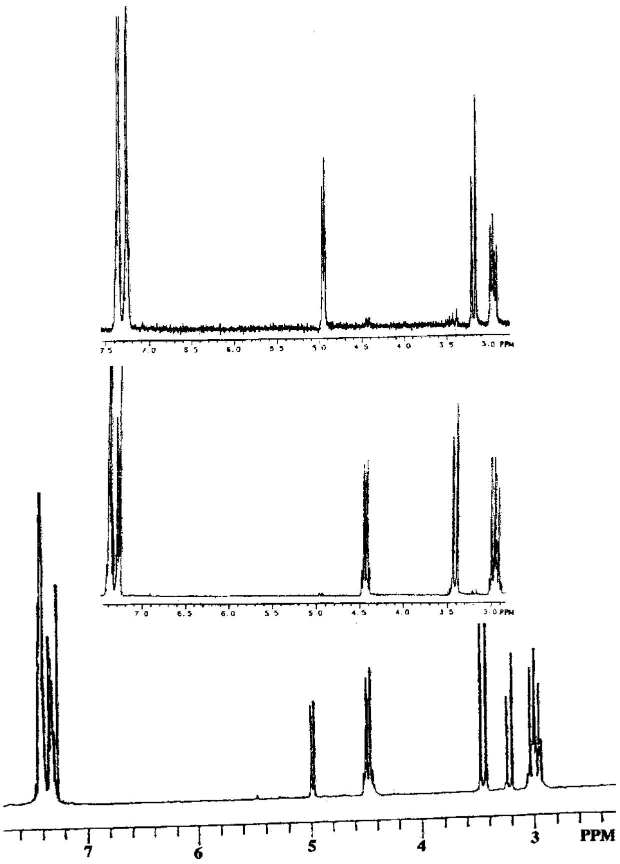
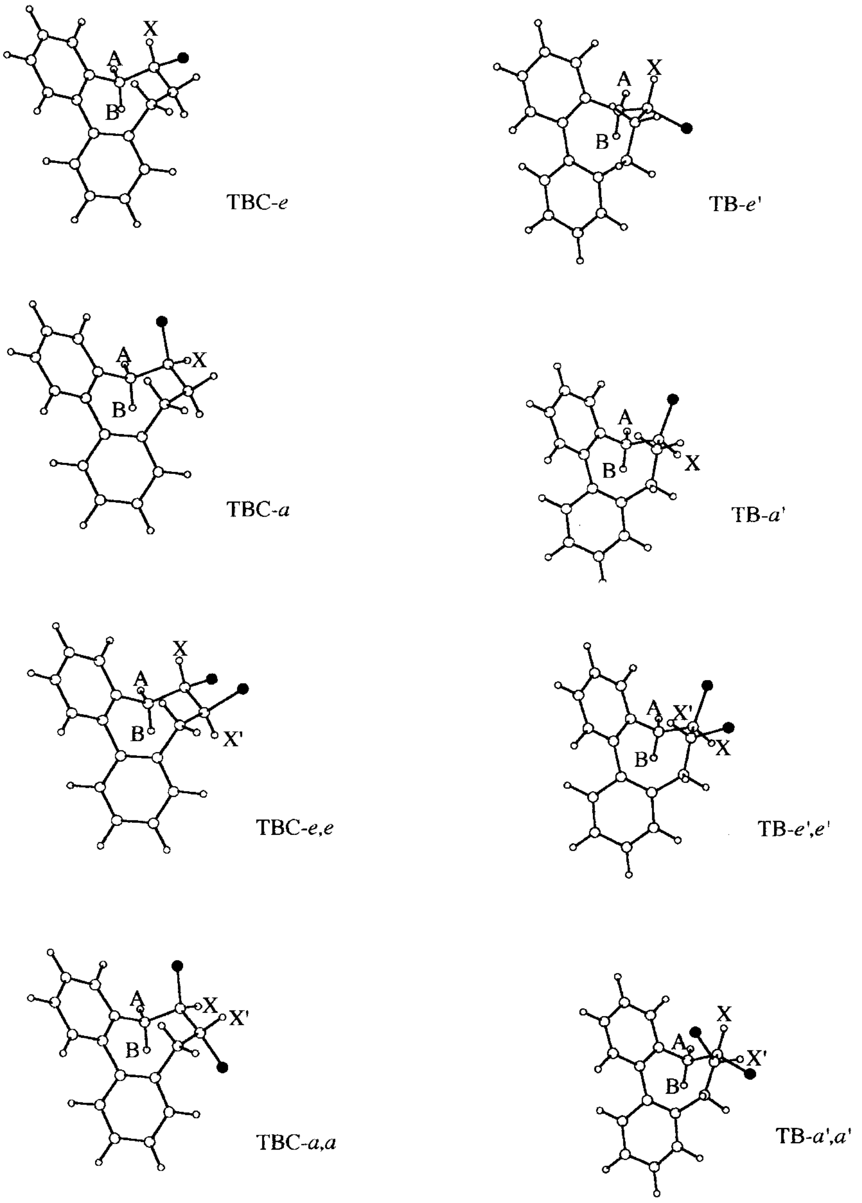


Figure 2. ^{1}H NMR spectra of *a,a* form (top), *e,e* form (middle) and equilibrated sample (bottom) of **2c**

Table 1. Experimental and calculated coupling constants (Hz) and calculated dihedral angles between AX, BX and XX′ protons (deg) in *e–a* and *e,e–a,a* forms of TBC and TB conformations in **1b** and **2b**. For labelling see Fig. 3

Conformation	ϕ_{AX}	$^3J_{calc}$	J_{exp}	ϕ_{BX}	$^3J_{calc}$	J_{exp}	$\phi_{XX'}$	$^3J_{calc}$	J_{exp}
TBC-*e*	82.7	2.02	1.3	−162.5	12.0	11.4			
TB-*e*′	−75.2	2.40		40.2	7.2				
TBC-*a*	−41.3	6.98	6.9	72.3	2.6	1.3			
TB-*a*′	47.2	6.0		163.4	12.1				
TBC-*e*,*e*	81.4	2.07	0.3	−164.4	12.58	11.6	−167.6	11.07	9.3
TBC-*e*′,*e*′	−74.7	2.44		40.2	7.2		−175.7	11.47	
TBC-*a*,*a*	−39.7	7.26	6.7	73.9	2.5	1.2	75.6	2.13	1.7
TBC-*a*′,*a*′	48.3	5.84		163.6	12.12		−69.2	2.6	



TBC-*e* TB-*e*'

TBC-*a* TB-*a*'

TBC-*e*,*e* TB-*e*',*e*'

TBC-*a*,*a* TB-*a*',*a*'

Figure 3. TBC and TB conformations of **1b** and **2b** in *e–a* and *e,e–a,a* forms. The dihedral angles between the A, B, X and X′ protons are used for calculation of the vicinal coupling constants of Table 1

Table 2. Observed coupling constants (Hz) for compounds **1** and **2** (solvent $CDCl_3$). For labelling see Fig. 3

Compound	Conformer	J_{AB}	J_{AX}	J_{BX}	$J_{XX'}$
1b	Maj (*e*)	−13.3	11.4	1.3	
	Min (*a*)	−13.8	6.9	1.3	
1c	Maj (*e*)	−13.2	11.6	0.5	
	Min (*a*)	−13.9	7.3	1.5	
1d	Maj (*e*)	−12.8	10.9	0.5	
	Min (*a*)	−13.8	7.8	0.5	
1e	Maj (*e*)	−12.6	11.0	1.7	
	Min (*a*)	−13.4	7.8	0.5	
2a	Maj (*e*,*e*)	−13.4	10.3	0.5	8.3
	Min (*a*,*a*)	−13.5	–[a]	1.7	–[a]
2b	Maj (*e*,*e*)	−14.0	11.6	0.3	9.3
	Min (*a*,*a*)	−14.4	6.7	1.2	1.7
2c	Maj (*e*,*e*)	−14.2	11.5	1.6	9.5
	Min (*a*,*a*)	−14.2	6.9	1.0	2.0
2d	Maj (*e*,*e*)	−13.4	10.7	0.5	11.2
	Min (*a*,*a*)	–[a]	–[a]	–[a]	–[a]
2e	Maj (*e*,*e*)	−13.7	10.7	0.5	11.4
	Min (*a*,*a*)	–[a]	–[a]	–[a]	–[a]
2f	Maj (*e*,*e*)	−13.0	10.6	0.5	11.0
	Min (*a*,*a*)	−13.7	6.8	1.7	–[a]

[a] Invisible either because of too low intensity or because of overlap by resonances of the major form.

solvent polarity. For compound **2c** the equilibrium constant is 0.47 in $CDCl_3$ and $(CD_3)_2CO$, 0.46 in C_6D_6 and 0.59 in CD_3OD, all at ambient temperature; however, the dipole moments of the *e*,*e* and *a*,*a* forms of **2c** calculated by AM1 show a marked difference (2.8 and 0.9 D respectively). The ΔG^O values in $CDCl_3$ were taken for comparison with the ΔE_{steric} values calculated by molecular mechanics and the ΔG values calculated by semiempirical methods. The heat of formation calculated by semiempirical methods, which is normally used for comparing conformational preferences, does not show any correlation with the experimental ΔG^O values for these compounds.

Molecular mechanics calculations predict the TBC-*e* and TBC-*e*,*e* forms to be lower in energy than the corresponding axial and axial–axial forms, except for the *trans*-dibromo compound **2c**. In most cases the calculated ΔE_{steric} values reproduce the experimental ΔG^O values (Table 3); for **1d** and **2b** the ΔE_{steric} value is underestimated. A regression coefficient of 0.93 and a standard deviation of 1.8 kJ mol^{-1} were estimated between the experimental ΔG^O and ΔE_{steric} values.

The effect of side chain conformations on the total steric energy of **1d, 1e** and **2d, 2e, 2f** was considered. The conformational space of the side chains was systematically searched by dihedral driving in both molecular mechanics and semiempirical methods. The numbers of rotamers found are given in Table 4. In some cases the

Table 3. Experimental ΔG^o values (^1H NMR, solvent $CDCl_3$) and ΔE_{steric} and ΔG values calculated by molecular mechanics and semiempirical methods for equatorial–axial equilibria (kJ mol^{-1}) of compounds **1** and **2**

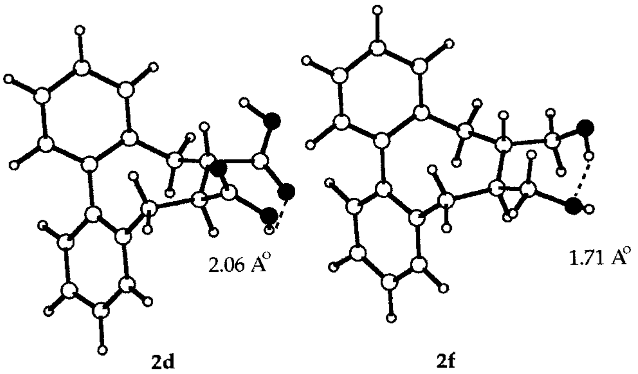
		ΔE(maj–min)	ΔG(maj–min)			
Compound	ΔG^o(maj–min)	MMP2-87	PM3	AM1	MNDO	MINDO/3
1b	−3.2	−3.0	−0.3	−0.4	−0.3	0.0
1c	−3.2	−3.1	−2.0	−0.6	−0.3	–
1d	−2.5	−0.1	−0.3	+0.8	−0.2	−0.9
1e	−1.4	−2.8	+0.6	+0.2	−0.3	−0.2
2a	−6.5	−5.6	+1.3	−1.1	−1.6	−2.4
2b	−3.2	−0.1	−0.2	−0.6	−0.7	−2.0
2c	−1.5	+0.4	−1.5	−1.0	−0.7	–
2d	−7.6	−6.5	−3.9	−2.4	−1.2	−0.5
2e	−7.9	−4.7	−3.3	−4.1	−1.9	−1.0
2f	−4.3	−4.4	−2.0	−1.8	−2.7	−2.2
R[a]		0.93	0.71	0.86	0.87	0.77
SD[b]		1.8	3.5	2.5	2.4	3.5

[a] R, regression coefficient.
[b] SD, standard deviation (k J mol^{-1}).

Table 4. Numbers of rotamers found for compounds with flexible side chain(s)

Compound[a]	MMP2-87	PM3	AM1	MNDO	MINDO/3
1d (*a*)	6	6	6	4	2
1d (*e*)	6	6	6	4	3
1e (*a*)	3	2	2	3	3
1e (*e*)	3	3	3	3	3
2d (*a*,*a*)	11	10	10	10	10
2d (*e*,*e*)	14	10	10	10	10
2e (*a*,*a*)	12	3	3	3	3
2e (*e*,*e*)	16	3	3	3	3
2f (*a*,*a*)	45	19	35	44	28
2f (*e*,*e*)	45	32	33	29	20

[a] (*e*), (*a*), (*e*,*e*) and (*a*,*a*) refer to the TBC-*e*, TBC-*a*, TBC-*e*,*e* and TBC-*a*,*a* conformations.



2d **2f**

Figure 4. One rotamer of each of **2d** and **2f** with an internal hydrogen bond

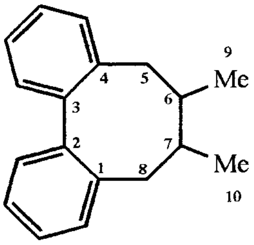
number of conformations found by molecular mechanics is more. The average $\Delta E_{\mathrm{steric}}$ and ΔG values were calculated by Boltzmann population analysis. In Table 3 the average values are given for **1d, 1e** and **2d, 2e, 2f**. The possibility of hydrogen bonding was considered in **2d** and **2f**. In **2d**, three rotamers with an internal hydrogen bond were found by AM1 and none by PM3. In **2f**, seven rotamers with a hydrogen bond were found by AM1, while PM3 calculations recognize a hydrogen bond in only three rotamers. Figure 4 shows one of the rotamers of each compound with the estimated hydrogen bond length.

The ΔG^{O} values are not reproduced correctly by semiempirical methods, except for compound **2c** calculated by the PM3 method. MNDO and MINDO/3 predict the TBC-*e* and TBC-*e*,*e* forms to be lower in energy than the corresponding axial and axial–axial forms (Table 3). Both methods underestimate the difference in energy between the two forms and the estimated values are far from the experimental ones. The standard deviations between the experimental values and those calculated by MNDO and MINDO/3 are 2.4 and 3.5 kJ mol^{-1} with regression coefficients of 0.87 and 0.77 respectively.

The AM1 method reproduces the order of stability of the two forms except for **1d** and **1e**. For **1d** and **1e** the stability of the *a* form is overestimated and for the other compounds the difference in ΔG between the two forms is underestimated. The standard deviation between the AM1-calculated values and the experimental ones is 2.5 kJ mol^{-1} with a regression coefficient of 0.86.

The PM3 method underestimates the energy difference

Table 5. Dihedral angles (deg) of eight-membered ring and 6 and 7 substituents in **2a** (TBC conformation) calculated by computational methods



Dihedral	Conformer	MMP2-87	AM1	PM3	MNDO	MINDO/3
1–2–3–4	*e*,*e*	59	58	60	63	59
	a,*a*	59	59	62	67	62
2–3–4–5	*e*,*e*	5	2	1	−1	−1
	a,*a*	1	1	0	−5	−5
3–4–5–6	*e*,*e*	−100	−98	−97	−92	−89
	a,*a*	−94	−96	−93	−86	−83
4–5–6–7	*e*,*e*	83	90	88	85	75
	a,*a*	77	84	84	81	76
5–6–7–8	*e*,*e*	−39	−58	−55	−54	−38
	a,*a*	−49	−49	−51	−50	−43

between the two forms in all but **1e** and **2a**, where the difference is overestimated. The dibromo compound **2c** is the only case estimated accurately by PM3. This might be due to the fact that PM3 is better parametrized for the bromine atom compared with the other semiempirical methods.[4] It is worth noting that the dibromo compound was the one overestimated by molecular mechanics calculations. A standard deviation of 3.5 kJ mol^{-1} was obtained between the experimental and PM3-calculated values with a regression coefficient of 0.71.

EXPERIMENTAL

The preparation of the compounds has already been described.[5] The ^1H NMR spectra were recorded with a Varian XL-300 spectrometer. The ΔG^O values were calculated from the ratio of the signals from 6-H of the mono- and 6-H and 7-H of the *trans*-di-substituted compounds. Calculation of the vicinal coupling constants in **1b** and **2b** (Table 1) was done by use of an equation described previously.[6]

Initial estimates of the geometry of structures **1** and **2** for semiempirical calculations were obtained by the MMX molecular mechanics method implemented in PCMODEL software.[7] Full minimization was done by using the semiempirical MINDO/3.[8] MNDO,[9] AM1[10] and PM3[4] Hamiltonians available in the MOPAC 6.0 computer program.[11] All the structures were characterized as stationary points and true minima on the potential energy surface using the keyword FORCE. A stationary point is described if the first derivatives of the energy with respect to changes in the geometry are zero. The criterion for a minimum is that all eigenvalues of the Hessian matrix are positive.[12] The dihedral angles of the eight-membered ring and the 6 and 7 substituents in **2a** in both forms calculated by semiempirical and molecular mechanics methods are given in Table 5.

The ΔG values were taken from the semiempirical calculations by combining the ΔH and ΔS values. No meaningful correlation was found between the experimental ΔG^O values and the ΔH_f values calculated by semiempirical methods.

The MMP2-87 molecular mechanics calculations[13,14] were performed using the interactive computer graphics program MOLBUILD.[15]. Systematic dihedral driving was performed on the side chain of **1d** and **1e** in steps of 15° length. For compounds **2d, 2e** and **2f**, two dihedral angles were driven for each side chain. Energy minima thus found in each were reoptimized further in the MMP2-87 and semiempirical methods.

Acknowledgement

P. R. R. is grateful to the Research Council of Tehran University for financial support.

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