A COMPARISON OF EMPIRICAL FORCE FIELD PARAMETERS
FOR MOLECULAR MECHANICS CALCULATIONS ON SATURATED HYDROCARBONS

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Abstract: Nine empirical force fields used in molecular mechanics calculations are
tested for their abilities to reproduce experimental geometric and energy data on
cis-syn-cis-perhydroanthracene.

The establishment of empirical force field (EFF) parameters, e.g., for bond
stretching, is of critical importance for molecular mechanics (MM) calculations on
organic compounds.[1] The kinds and actual values of the parameters, as well as the
iteration methods used in various MM procedures, differ in significant ways, making
it difficult to evaluate the performance of extant force fields.

A good test of EFF parameters is to find out how well they reproduce experi-
mental data that were not available at the time that these parameters were
adopted.[2] Saturated hydrocarbons are of primary importance in defining and testing
the core EFF force-field parameters (i.e., those for hydrogen and tetracoordinated
carbon). A good test hydrocarbon is syn-cis-syn-perhydroanthracene (**1**), which has
the important characteristic of being rather rigid and of having an ordered crystal
phase.[3] A highly accurate structure of **1** has recently been obtained from low
temperature X-ray diffraction data.[4] This molecule has a 1,3 diaxial interaction
and this strain is of the same type as that in a 1,5 (+)gauche-(-)gauche $(CH_2)_5$
unit, a feature which is present in many medium-ring compounds.[5] The barrier to
ring inversion in I has been measured by dynamic NMR[6,7] and the mechanism of the
inversion process has been established by molecular mechanics calculations[7] with
the EAS (Schleyer)[8] force field (Figure 1). Some calculations have also been done
on **1** with the MM2 (Allinger)[9] parameters.[4]

The transition state for ring inversion in **1** has large angle and torsional
strains, which are also common in the conformations of medium rings. Since our
previous molecular mechanics calculations[10] on medium ring compounds made use of
the Boyd program and force field,[11] we have re-examined **1** and its ring inversion
transition state using not only this and the EAS and MM2 force fields, but also
those developed by Bartell[12] (MUB2, as well as a modified[13] version of MUB2),
Ermer and Lifson,[14] White and Bovill,[15] Rasmussen,[16] and Ōsawa (MM2' version of

MM2)[17]. All these EFF's have the usual terms for bond stretching, angle bending, 3-fold torsional barriers, and non-bonded (1,4 or higher) potentials (6-9, or 6-12, or exponential-6). Terms (for saturated hydrocarbons) present in only some EFF's include charges on C and H,[16] 1,3 non-bonded potentials,[12,13] cubic or higher-order stretch or bend terms and/or cross-interaction terms,[8,9,12-14,17] and 1- and 2-fold torsional potentials.[9,17] The present calculations were done with the versatile DELPHI MM program of van de Graaf and Baas.[18]

We have chosen to focus on the two quantities ($R_{1,8}$ and $\theta_{8a,9,9a}$) shown in Figure 1a and on the inversion energy barrier (Figure 1b), as other experimental data on 1 are fitted well by all the EFF's. The experimental $\Delta G^{\ddagger}$ has been obtained[7] with $\kappa = 1/2$ in the Eyring equation and thus corresponds to the process, 1-CCC $\rightarrow$ racemic 1-CTC, in Figure 1b.[19] The $\Delta G^{\ddagger}$ (1-CCC $\rightarrow$ one enantiomer of 1-CTC) is larger by RTln2 (0.33 kcal/mol at -30° C), and $\Delta G^{\ddagger}$ + RTln2 is the quantity that should be compared to ΔSE, the strain energy difference between the ground and transition state conformations. For EFF's that have been designed to fit $\Delta G^{\ddagger}$'s via the calculation of zero point energies, etc., the difference between the experimental and the appropriately calculated $\Delta G^{\ddagger}$'s are given in Figure 2, and are more relevant than the former quantities, which, nevertheless, are also shown (unfilled bars), as ΔSE values have somtimes been used even for these EFF's. The three different kinds of error bars in Figure 2 are scaled so that 0.1 Å, 1°, and 1 kcal/mol give the same bar lengths. These scaling factors are considered to be appropriate, even though they are arbitrary, and have no generality.

Figure 2 shows the performance of the nine force fields in terms of deviations (i.e., errors) between calculated and experimental values. Our results with the EAS and MM2 EFF's agree with those already published.[4,7] There is a tendency for EFF's to fit well either the geometry or the energy barrier of 1, but not both. Little relationship seems to exist between the performance and the complexity of the force fields in the present case, a point which has been made before.[20]

We make two comments about the geometry of 1. First, the very slight distortion from $\underline{C}_s$ symmetry in the crystal arises because of the lack of site symmetry; the calculated distortion energy is only ca 25 cal/mol (Boyd EFF).[21] Secondly, the short H...H distance found in 1-CCC can be compared with other data for sterically compressed molecules.[22] Since X-ray data give the positions of electron densities, rather than of nuclei, it is necessary to lengthen the apparent C-H bond lengths to about 1.09 Å.[22,23] The corrected short H...H distance in 1 is then 1.92 ± 0.04 Å (the uncorrected value is 2.08 Å); the Boyd and MUB2 force fields give 1.96 and 1.82 Å respectively. This is quite a short distance, the van der Waals separation being 2.4 Å, but even shorter non-bonded H...H distances are known.[22]

Our conclusion is that the force fields for saturated hydrocarbons likely can be improved by the consideration of recent geometric and energy data on selected strained hydrocarbons, such as 1 and certain medium rings.[10] Overall, for 1, the Boyd EFF does the best, followed by the White-Bovill, Ermer-Lifson, and MM2 EFF's.
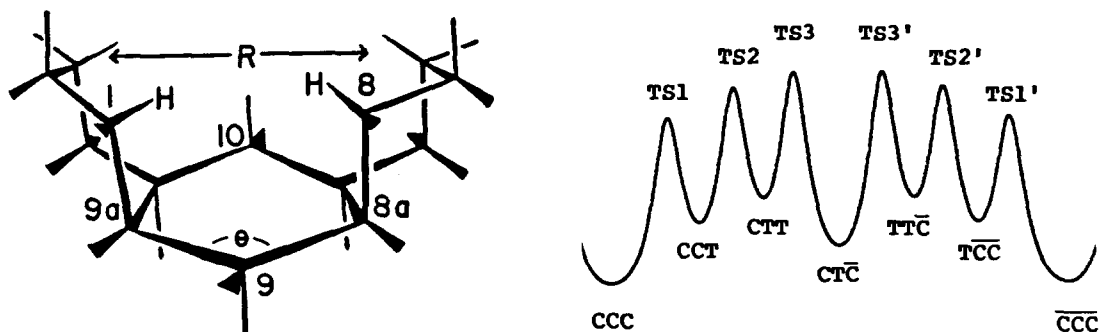
(a) **1-CCC** $R_{exp} = R_{1,8} = 3.396 \pm 0.002$ Å   (b)

$\theta_{exp} = \theta_{8a,9,9a} = 116.1 \pm 0.1°$

Figure 1. (a) 1-CCC as viewed from a point nearly on its symmetry plane, which passes through C-9 and C-10 (the data shown are from X-ray work[4]).

(b) One of the two mirror-image related paths for ring inversion of 1-CCC to 1-$\overline{CCC}$,[7] (C = chair, T = twist-chair). **TS1** and **TS1'**, etc., differ only in the labelling of identical atoms; CT$\overline{C}$ has $\underline{C}_2$ symmetry and is chiral.

(ENERGIES IN KCAL/MOL)

	BOYD	ERMER-LIFSON	RASMUSSEN
$R_{calc} - R_{exp}$ (Å)	0.08	0.10	0.34
$\theta_{calc} - \theta_{exp}$ (°)	0.5	0.2	3.3
$\Delta SE - (\Delta G^{\ddagger} + RTln2)$	0.7	3.5	-2.7
$\Delta G^{\ddagger}_{calc} - \Delta G^{\ddagger}$	-0.6	1.9	-2.0
SE (1-CCC)	13.0	16.0	-19.2

	WHITE-BOVILL	ALLINGER MM2	$\overline{O}$SAWA MM2'
$R_{calc} - R_{exp}$ (Å)	0.09	0.13	0.08
$\theta_{calc} - \theta_{exp}$ (°)	0.20	0.8	0.3
$\Delta SE - (\Delta G^{\ddagger} + RTln2)$	-1.3	-1.2	3.7
SE (1-CCC)	12.0	23.8	24.0

	SCHLEYER EAS	BARTELL MUB2	MODIFIED MUB2'
$R_{calc} - R_{exp}$ (Å)	0.21	-0.01	-0.01
$\theta_{calc} - \theta_{exp}$ (°)	1.4	-0.3	-0.2
$\Delta SE - (\Delta G^{\ddagger} + RTln2)$	-1.6	7.3	5.9
SE (1-CCC)	20.0	948.1	947.8

Figure 2. Performance of various force fields. The "absolute" strain energies (SE's) of 1-CCC have only numerical significance and cannot be compared.

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2. The standard deviation of the fit of MM calculations for a large number of molecules is often used as a test, but this tends to hide errors. The largest deviation in the fit is generally a more significant number, in our opinion.

3. Unfortunately, many important hydrocarbons are either liquids or have disordered crystalline phases and thus accurate geometric data are often unavailable.

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19. Since TS2 and TS3 have similar kinds of strain, the calculated energy difference between them almost certainly has the correct sign and magnitude. With TS2 more stable than TS3 by 0.4 to 1.4 (mean of 0.8) kcal/mol, only TS3 and TS3' (and their mirror images) are kinetically significant. The calculated entropy of activation (ca 2.5 eu) is in fair agreement with the experimental value (-0.3 ± 1 eu,[6] but where possible systematic errors[5] are not included).

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