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1 AUTHOR:

Gabor I. Csonka
Budapest University of Technology and E…

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Analysis of the Core-Repulsion Functions Used in AM1 and PM3 Semiempirical Calculations: Conformational Analysis of Ring Systems

G.I. Csonka

Department of Inorganic Chemistry, Technical University of Budapest, H-1521 Budapest, Hungary

The AM1 and PM3 potential energy surfaces of cyclopentane have been compared and the energy difference between two (boat and chair) cyclohexane conformers analyzed. The effects of reparameterization and different core-repulsion functions (CRFs) have been studied. The H—H, C—H, and C—C CRF energy contributions have been calculated separately. The results show that the CRF energy corrections stabilize the correct (MM2 and *ab initio*) geometries. The PM3 equilibrium geometry of cyclopentane is closer to the MM2 and *ab initio* results than the AM1 geometry. It is known that above 190 pm the AM1 H—H CRF curve is smooth and negative but the PM3 H—H CRF curve has a trough and a shoulder. It has been shown that this latter oscillation is not damped by other parameters. As a result, the H—H PM3 energy gradient curve is different from the quasilinear AM1 and *ab initio* gradient curves. © 1993 by John Wiley & Sons, Inc.

INTRODUCTION

Recently, Ferguson et al.[1] examined the potential energy surfaces of cyclic alkanes using molecular mechanics (MM2[2]), semiempirical (AM1[3]), and *ab initio* (RHF/3-21G[4]) methods to determine if they produce consistent results. They investigated the source of any errors between the methods. It was found that the MM2 and *ab initio* results are consistent in the relative energies and geometries. The AM1 geometries were consistent with the other methods but the relative energies were not. The cyclopentane was the only exception. In this case, even the AM1 geometries were different. An energy decomposition analysis indicated that the disparities are mainly due to errors in the one-center energies of the AM1 calculations. The optimization of all parameters of the one-center energy components was proposed to remedy this problem. The authors suspected that the AM1 core-repulsion function (CRF) is producing anomalies. They supposed that a minimum in the attractive Gaussian of CRF at 210 pm for H—H interactions partly explains the near planarity of AM1 cyclopentane equilibrium geometries and the underestimation of relative energy of the boat structure of cyclohexane.

All above-mentioned methods have advantages and disadvantages. The MM methods are the computationally least intensive, but they require a large number of carefully obtained parameters (up to four atomic terms) for new systems of interest. An appropriately parameterized MM method is capable to give correct geometries and relative conformational energies and energy barriers. However, it is not possible to represent molecular orbital (MO) interactions with MM calculations, which may play a role in the enzyme–substrate interactions (frontier orbital interactions, charge density) or in any other area of the chemistry where MOs and the related (ionization potential) or derived (molecular electrostatic potential, spin density) quantities play a role.

The *ab initio* and semiempirical methods are MO methods. The *ab initio*, having no need for empirically determined parameters, is the more theoretically pure, but it is computationally intensive, slow, and limited to molecules containing relatively few heavy atoms. A semiempirical method uses empirical parameters, so its accuracy is limited to the accuracy of the experimental data used in obtaining parameters. Another problem is that the parameters should be fully optimized using an overdetermined set of molecules. Otherwise, it is not possible to partition errors in calculated quantities between deficiencies in the model and incompleteness of the optimization of the parameter set.[5,6] To obtain the best fully optimized semiempirical parameter set is a difficult task. Dewar et al. states, "The main problem in developing treatments such as AM1 is not the actual determination of parameters but determining the best forms of parametric functions and finding the best minimum on the parameter hyper surface. Our very extensive experience has indicated that the best minimum cannot be found reliably by simple minimisation of the error function..."[7] Despite those serious problems, the semiempirical methods are accurate and fast enough for applications to large

chemical systems (~100 atoms). The semiempirical methods, based upon the neglect of diatomic differential overlap (NDDO) approximation—such as MNDO,[8] AM1, and PM3[5,6] parameterizations—became popular because of their chemically useful accuracy. It was shown that the accuracy of semiempirical methods may be comparable with that of large basis set *ab initio* results.[3]

It was found that there were problems with the MNDO parameterization in describing the conformation of crowded molecules. Later, the AM1 parameterization tried to fix those problems by introducing the CRFs and new parameters. The CRFs are outside the quantum-mechanical framework. Their role is to correct the nuclear–nuclear repulsion and exchange repulsion energy terms. The results were better, but the problems were not completely eliminated. The AM1 CRF for hydrogen is composed of three Gaussians.[3] The function has a maximum at 110 pm and a root at about 190 pm and a minimum at 230 pm. The existence of this minimum seems to support the explanation of Ferguson and coworkers.[1]

Recently, a new parameter set (PM3) was introduced in which all the parameters have been fully optimized and the CRFs have been composed of two Gaussians. In the case of hydrogen, the centers of Gaussians are at 153.75 and 157.02 pm and their maxima are 1.1288 and −1.0603, respectively. The resulting function has a maximum at 120 pm, a minimum at 180 pm, and a maximum at 200 pm.[9] Contrary to the AM1 CRF, the PM3 CRF is repulsive in the whole space. The chemically interesting H—H distances are above 170 pm (170–180 pm is the methyl and methylene H—H distance). The vicinal H-C-C-H distances range between 230–310 pm. There is a gap between the two region because those H—H distances between the two are much less frequent. The shape of the AM1 and PM3 CRFs agree well in the range of 160–170 pm but there is a large disagreement in the region around 200 pm. The minimum at 180 pm and maximum at 200 pm of the PM3 curve seems to be rather artificial, which may unphysically distort the energy surface.[9]

The existence of different parameterizations of the same semiempirical model provides a good opportunity to study the effect of the parameters and differentiate between the parameter-dependent and -independent predictions of the model. This way, the sources of errors may be discovered more easily. In the case of contradiction, a good-quality *ab initio* calculation on simple model compounds may decide which parameterization is better.

In the present article, the AM1 and PM3 energy surfaces of cyclopentane have been compared and the energy difference between two cyclohexane conformers analyzed to check the need of reparameterization[1] and effects of the CRF. The H—H, C—H, and C—C CRF energy contributions have

been calculated separately to show which conformer is stabilized by the CRF energy. The H—H AM1 and PM3 energy gradients have been compared to each other and to HF and MP2 gradients to show the effects and distortions introduced by the PM3 CRF.

METHODS

All geometries were fully optimized with the semiempirical AM1 and PM3 methods using adapted versions of the MOPAC 6.0[10] program. The program was modified to calculate and print the CRF energy components. For *ab initio* calculations, the CADPAC 4.2[11] program was used. For force-field calculations, the MM2[2] program was applied. The calculations were carried out on an i486/33-MHz workstation and on an IBM RS/6000 model 320H. All geometry optimizations were done without symmetry constraints and with the PRECISE keyword of MOPAC. The fully optimized geometries were always verified as local minima by establishing that their Hessian matrices are positive definite or as transition states with one negative eigenvalue.

RESULTS

Figure 1 shows the AM1 energy hypersurface of the cyclopentane around the minimum. Two vicinal dihedrals (α and β) are suitable to describe all possible conformations (all five atoms are included in two vicinal dihedrals). A single conformation may be represented by five neighboring dihedral pairs. The largest pair is selected for unique representation. The signs of the dihedral angles are opposite if the two noncommon carbon atoms are on the same side of the plane defined by the three common atoms in the
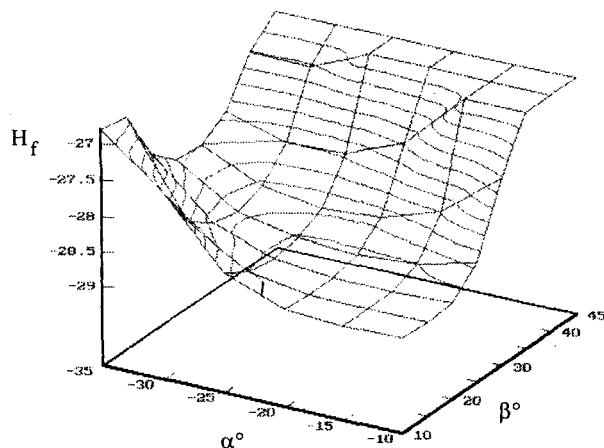

Figure 1. AM1 energy hypersurface of cyclopentane in function of two vicinal dihedral angles. The heats of formation (H_f) are given in kcal/mol. The values with more than 2 kcal/mol above the minimum were taken as $H_{f\min} + 2$.

Figure 2. PM3 energy hypersurface of cyclopentane in function of two vicinal dihedral angles. The heats of formation (H_f) are given in kcal/mol. The values with more than 2 kcal/mol above the minimum were taken as $H_{f\min} + 2$.
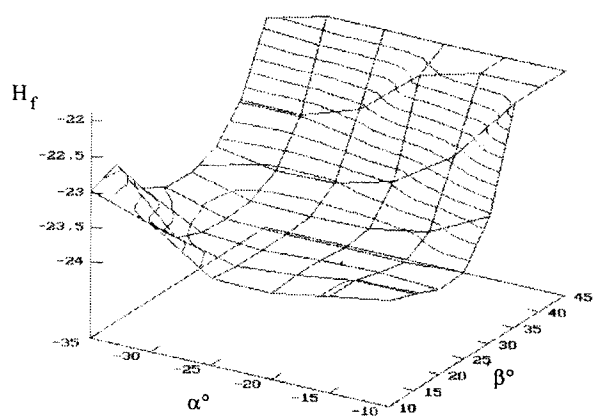
two dihedrals. In the envelope conformation, the absolute values are equal to each other. The energy valley is flat around the envelope minimum point ($\alpha = -16.25°$, $\beta = 16.25°$, and the heat of formation $H_f = -28.793$ kcal/mol) and the energy of the planar conformation is only slightly higher (less than 0.020 kcal/mol).

Figure 2 shows the PM3 energy hypersurface in function of the same dihedral angles. The PM3 parameterization results in less planar molecular geometry ($\alpha = -29°$, $\beta = 25°$, and $H_f = -23.88$ kcal/mol), which is closer to the MM2 and *ab initio* geometries given in ref. 1 and reproduced in this work for comparison purposes.

The 1,2 H—H distances in cyclopentane range from 230 pm (planar) to 250 pm (puckered). In AM1 (nearly planar) equilibrium geometry, all 1,2-diaxial hydrogen distances are 230 ± 1 pm. The minimum on the H—H CRF close to 230 pm may help explain the anomalous AM1 geometry.[1] However, the CRF energy difference is less than 0.07 kcal/mol, as the CRF is nearly constant between 230–250 pm, and other H—H interactions may contribute considerably to the total H—H CRF energy. Drawing conclusions from several H—H interactions can be misleading. Consequently, the whole H—H CRF energy was calculated.

Table I show CRF energy components' influence on the stability of equilibrium conformations of cyclopentane. The AM1 and PM3 heat of formations and CRF energy components (H—H, C—H, and C—C) were calculated in MM2 equilibrium geometry and in AM1 and PM3 equilibrium geometries. The results

show that the total CRF energy is not stabilizing the more planar molecular geometries. In the AM1 calculations, the H—H CRF energy difference is positive. The suspicion of Ferguson et al.[1] cannot be justified: that the CRF energy contributions stabilize the correct, nonplanar MM2 geometry. The effect is too small in the case of AM1 parameterization while it is much larger in the case of PM3 parameterization and the PM3 geometry is better. The PM3 CRF is considerably more positive than the AM1 CRF in the 230- to 250-pm range, and it is expected that the PM3 optimum geometry of cyclopentane is less planar than the AM1 one. The calculated results support the expectations.

In the case of cyclohexane, the AM1 energy difference of two (chair and boat) conformers (3.52 kcal/mol) is too small compared to experimental (and MM2) values of 5.9 ± 0.6 kcal/mol.[12] The corresponding PM3 energy difference is 4.44 kcal/mol. Table II shows the CRF energy components of various interactions. The AM1 H—H CRF result does not agree with the result of Ferguson et al.[1] so the calculations were repeated with a different algorithm using the H—H distance matrix. The results were identical. Even the H—H CRF interaction energy stabilizes the AM1 boat conformer. The stabilization effect of total AM1 CRF energy difference is not negligible compared to the whole energy difference. The PM3 CRF is even better.

The results show that, in contrary to the proposition of Ferguson et al.,[1] the CRF energy contribution corrects the energy in the correct sense and other effects are responsible for the nonsatisfactory results (the corrections are too small in the case of AM1). The use of fully optimized one-center parameters (PM3) does not eliminate all the errors in the case of cyclopentane, but the resulting conformation is less planar.

The artificial and supposedly unphysical behavior of H—H PM3 CRF may be the origin of strange H—H stabilization effects. Several examples of those stabilizations have been published,[9] but it was no possible to check them experimentally. To overcome this difficulty, precise *ab initio* calculations were performed on the H_2 molecule, the simplest model possible. The effect of the trough and shoulder on the H—H PM3 CRF may be compensated by other parameters. This possibility has been checked against AM1, *ab initio* [HF/6-31G(p) and MP2/6-31G(p)] calculations. The total energy of two hydrogens was calculated in the function of H—H distance between 1.4 and 2.5 pm. Figure 3 shows the

Table I. CRF energy differences in cyclopentane.

ΔE	H—H	C—H	C—C	Total
$E_{AM1//AM1} - E_{AM1//MM2}$	0.168	2.246	−2.244	0.170
$E_{PM3//PM3} - E_{PM3//MM2}$	0.710	0.929	−0.194	1.445

Energies in kcal/mol. $E_{model//geometry}$.

Table II. CRF energy differences in cyclohexane.

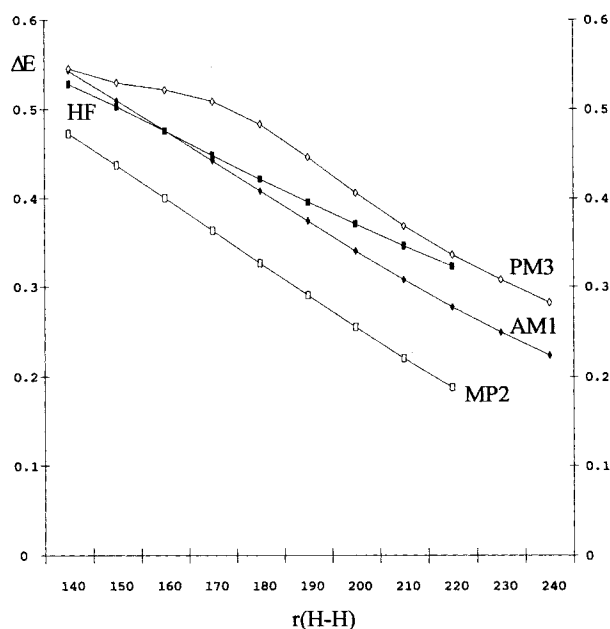| ΔE(boat-chair)	H—H	C—H	C—C	Total
AM1	0.410	0.839	−0.461	0.788
PM3	1.226	0.378	−0.205	1.399

Energies in kcal/mol.

Figure 3. AM1, PM3, and *ab initio* HF and MP2 energy difference (eV) as the H—H distance varies between 140 and 250 pm with steps of 10 pm. (-□-), MP2; (-■-), HF; (-◆-), AM1; (-◇-), PM3.

energy differences as the H—H distance increases by 10 pm [$\Delta E(\Delta r)$, $\Delta r = 10$ pm]. The ΔE value at 140 pm is the energy difference between $E(150$ pm) and $E(140$ pm) and so on. Figure 3 shows that the AM1 and *ab initio* energy first derivative is quasi-linear in that interval. The minimum on the AM1 CRF curve does not influence the linearity (it is smooth and compensated by other parameters). The PM3 energy derivative is nonlinear, and the most serious problems are expected in the region of 160–200 pm. This is in agreement with results of Buss et al.[9] In PM3 parameterization, the rapid changes of CRF are not compensated by other parameters.

The functional analysis of PM3 C—H CRF shows again the existence of two maxima and a minimum similarly to H—H CRF.

CONCLUSION

In AM1 and PM3 semiempirical calculations for the cyclopentane and cyclohexane conformers, the CRF energy contributions make preferable the correct geometries. They always bring the energy difference of the conformers closer to the MM2 and *ab initio* results. This result does not agree with earlier suspicions.[1] Full optimization of one-center parameters (PM3) gives better a result for cyclopentane (together with more important CRF contribution) but does not reproduce the MM2 and *ab initio* results. There are minimum and maximum points on the PM3 H—H CRF that do not seem to have any physical meaning, and their distortion effect on the energy function is not compensated by other parameters. The origin of this is the use of two Gaussians with opposite signs. A single Gaussian with different exponents below and above the center would provide a smooth energy function. In this region, there must be a relatively small number of experimental data because it is in the gap of geminal and vicinal H—H distances. Probably, this small effect will not cause serious problems, but it stresses that parameterization based only on experimental results can lead to strange physical behavior in regions where no or a small number of experimental data are available. *Ab initio* calculations may help fix those problems.

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