

Improved AMBER* torsional parameters for the N–N rotational barrier in diacylhydrazines

Subhas Chakravorty and Charles H. Reynolds*

Rohm and Haas Company, 727 Norristown Road, Spring House, PA 19477-0904

The structure and rotational barrier for substituted diacylhydrazines are of significant interest given the role this functionality plays in peptidomimetics and ecdysone agonists, the latter of which have application as extremely selective insecticides. Ab initio calculations show that the lowest energy conformations are typically nonplanar with essentially perpendicular nitrogen lone pairs. Molecular mechanics calculations using the AMBER force field in MacroModel yield minima and rotational barriers that are both quantitatively and qualitatively inconsistent with the ab initio results. In this work the AMBER* N–N rotational barriers for all configurations of the parent, methyl and di-methyl substituted diformylhydrazines have been fitted to MP2/6-31+G** relative energies. The resulting AMBER* torsional parameters have been validated by calculating the rotational barriers for N-t-butyl substituted diformylhydrazine, dibenzoylhydrazine and an azadipeptide. In each case the new AMBER* rotational barriers compare favorably with the corresponding MP2 calculated rotational barriers. © 2000 by Elsevier Science Inc.*

INTRODUCTION

Diacylhydrazines represent an important structural class of chemistry given the role this functionality plays in peptidomimetics^{1–7} and nonsteroidal ecdysone agonists.^{8–13} The latter have proven to have significant commercial importance as extremely safe and selective insecticides.^{8–11} Extensive ab initio calculations performed by Reynolds and Hormann¹⁴ for diformylhydrazine and a few simple derivatives (**1–3**) demonstrated that these structures are intrinsically nonplanar with

nearly perpendicular nitrogen lone pairs. In contrast many force fields, including AMBER*,^{15–17} give structures that are planar with the minimum at either 0 or 180°. This is most likely because the OC–N–N–CO torsional parameters have been parameterized to reproduce the crystal structure of diformylhydrazine, which is reported^{18–21} to have a planar OC–N–N–CO dihedral angle. Reynolds and Hormann¹⁴ have argued that the diformylhydrazine crystal structure is not representative of the class, and is only planar because of favorable crystal packing forces.

Comparison of AMBER* with high quality ab initio calculations (Tables 1 and 2) show that AMBER* not only gives a quantitatively inaccurate accounting of the ground state structure and N–N rotational barrier in diacylhydrazines, but the results are not even qualitatively correct (i.e. the ab initio minimum is a maximum using molecular mechanics). Since we have a strong interest in modeling diacylhydrazines, we have set out to develop a set of improved AMBER* torsional potentials for this structural class. These improved parameters can be integrated into any standard molecular modeling package such as MacroModel Version 6.0.²²

Recent reviews^{23,24} discuss several methods for parameterization and augmentation of existing molecular mechanics force fields. In the case where additional force field parameters are needed for molecules for which little or no experimental data exists it has become increasingly common to use high level ab initio calculations to generate the necessary reference values.^{23,25} We have chosen to fit our torsional parameters to reproduce MP2/6-31+G** relative energies. Previous work¹⁴ indicates that a correlated wavefunction is necessary, and MP2/6-31+G** provides a reasonable compromise between accuracy and speed. One approach for calculating the ab initio reference data would be to generate the fully optimized MP2 potential surfaces directly. The structures and energies from the ab initio calculations could then be used as the reference state for optimization of the force field parameters. One limitation of this approach is that geometry optimizations at the MP2 level with a sufficiently large basis set are very expensive. An alternative is to derive the new parameters by iteratively fitting

*Corresponding author: C.H. Reynolds. R.W. Johnson Pharmaceutical Research Institute, Welsh and McKean Rds., Spring House, PA 19477-0776. Tel.: 215-619-5482; fax: 215-641-7857.

E-mail address: CReynoll@prius.jnj.com.

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Table 1. Selected relative rotational barriers for N-substituted diformylhydrazines 1-3 in kcal/mol

Structure	Dihedral	AMBER* original	Error ^a	AMBER* modified	Error ^a	MP2 ^b single point	MP2 ^c optimal
1a (H,H)	0	21.1	3.3	22.3	4.5	17.8	17.0
	90	25.7	25.6	0	-0.1	0.1	0
	180	0	0.0	3.5	3.5	0	0.8
1b Z,E	0	5.7	-6.8	12	-0.5	12.5	10.8
	90	19.0	19.0	0	0.0	0	0
	180	0	-7.4	6.3	-1.1	7.4	7.3
1c E,E	0	2.8	-13.6	11.0	-5.4	16.4	15.0
	90	16.6	16.6	0	0.0	0	0
	180	0	-14.4	8.3	-6.1	14.4	12.3
2a (Me,H)	0	19.1	-1.1	22.3	2.1	20.2	
	90	15.7	15.7	0	0.0	0	0
	180	0	-4.7	5.1	0.4	4.7	7.0
2b Z,E	0	3.1	-10.5	12.0	-1.6	13.6	
	90	15.8	15.8	0	0.0	0	
	180	0	-13.4	8.9	-4.5	13.4	
2c E,E	0	1.2	-14.9	10.3	-5.8	16.1	
	90	14.8	14.8	0	0.0	0	
	180	0	-13.0	9.2	-3.8	13.0	
2d E,Z	0	5.0	-6.6	11.4	-0.2	11.6	
	90	17.9	17.9	0.0	0.0	0.0	
	180	0.0	-6.0	6.4	0.4	6.0	
3a (Me,Me)	0	13.7	-6.3	24.7	4.7	20.0	
	90	8.7	8.7	0	0.0	0	0
	180	0	-12.9	16.4	3.5	12.9	19.1
3b Z,E	0	3.0	-11.4	18.2	3.8	14.4	
	90	10.8	0	0.0	0		
	180	0	-13.3	17.4	4.1	13.3	
3c E,E	0	1.0	-11.2	17.3	5.1	12.2	
	90	10.1	10.1	0	0.0	0	
	180	0	-12.8	18.0	5.2	12.8	
			Rms error:		3.1		
			unsign.avg:		2.2		

^aError relative to the MP2 single point energies in kcal/mol.^bMP2 single point energies for the final iteration.^cValues taken from Reynolds and Hormann.¹⁴

the ab initio rotational barrier evaluated at the classical geometries obtained by the modified force field. This approach is more efficient if only a few iterations are needed. Norrby et al^{26,27} and Hagler et al^{28,29} have both shown that the iterative method is very effective for determining missing torsional parameters within the context of an existing force field. This iterative approach, using the computationally more tenable single point quantum calculations, can provide force field parameters with an accuracy comparable to using the fully optimized quantum calculations at a much lower cost. For example, it takes approximately 23 times more cpu time to completely minimize the parent diformylhydrazine (**1**) at the MP2/6-31+G** level compared to a single point calculation at the same level. Our intention was to make the fewest changes necessary to the default AMBER* forcefield. Therefore, we kept all other parameters, including the partial charges, constant.

PARAMETRIZATION METHOD

The AMBER* X-N(sp²)-N(sp²)-Y torsional parameters for diacylhydrazines were derived by iteratively fitting them to the ab initio MP2 single point energies as described below:

1. Optimize geometries using modified AMBER* parameters from previous iteration (original AMBER* used for first iteration).
2. Calculate MP2 single point energies with 6-31+G** basis set at critical points on the torsional potential surface using Gaussian98³⁰ on a Silicon Graphics R10000 class workstation.
3. Fit AMBER* torsional potentials to the MP2 single point surface.
4. Repeat steps 1-3 until parameters are converged (i.e. no significant change)

Table 2. Ab initio single point energies^a in Hartrees

Structure	Dihedral	MP2/6-31+G**	Structure	Dihedral	MP2/6-31+G**
1a (H,H)	0	−337.600409	4d	0	−494.342338
	90	−337.628548		90	−494.362665
	180	−337.628730		180	−494.344767
1b	0	−337.606463	5a (<i>tert</i> -Bu,Me)	0	−533.509982
	90	−337.626332		90	−533.545643
	180	−337.614610		180	−533.513146
1c	0	−337.598966	5b	0	−533.512904
	90	−337.625054		90	−533.545024
	180	−337.602039		180	−533.501426
2a (Me,H)	0	−376.774985	5c	0	−533.518680
	90	−376.807243		90	−533.545257
	180	−376.799801		180	−533.512266
2b	0	−376.785122	5d	0	−533.513630
	90	−376.806841		90	−533.545637
	180	−376.785520		180	−533.513160
2c	0	−376.778921	6a	0	−510.363568
	90	−376.804482		90	−510.391828
	180	−376.783725		180	−510.383188
2d	0	−376.785835	6b	0	−510.344838
	90	−376.804319		90	−510.372730
	180	−376.794813		180	−510.369175
3a (Me,Me)	0	−415.954855	6c	0	−510.347831
	90	−415.986795		90	−510.385994
	180	−415.966241		180	−510.364310
3b	0	−415.962756	6d	0	−510.351997
	90	−415.985751		90	−510.389499
	180	−415.964517		180	−510.370750
3c	0	−415.965546	7a	0	−955.047232
	90	−415.984911		90	−955.084292
	180	−415.964570		180	−955.046003
4a (<i>tert</i> -Bu,H)	0	−494.332610	7b	0	−955.061555
	90	−494.367652		90	−955.075131
	180	−494.347458		180	−955.052697
4b	0	−494.339364	7c	0	−955.035397
	90	−494.366573		90	−955.074868
	180	−494.324509		180	−955.053163
4c	0	−494.334496	7d	0	−955.036534
	90	−494.363418		90	−955.078136
	180	−494.323782		180	−955.047103

^a For the final iteration.

Convergence was achieved after only three iterations.

All four configurations (Z,Z; Z,E; E,E and E,Z) of diformylhydrazine (Figure 1) and its N-methyl derivatives (**1–3**) were considered in fitting the force field parameters.

The AMBER* force field energy for a molecule, E_{AMBER^*} , may be written as a sum of the following terms:

$$E_{\text{AMBER}^*} = E_{\text{stretch}} + E_{\text{bend}} + E_{\text{torsion}} + E_{\text{vdW}} + E_{\text{electrostatic}} \quad (1)$$

and, specifically the E_{torsion} can be written as:

$$E_{\text{torsion}} = \sum_{\text{dihedrals}} \frac{V_n}{2} [1 + \cos(n\phi - \gamma)] \quad (2)$$

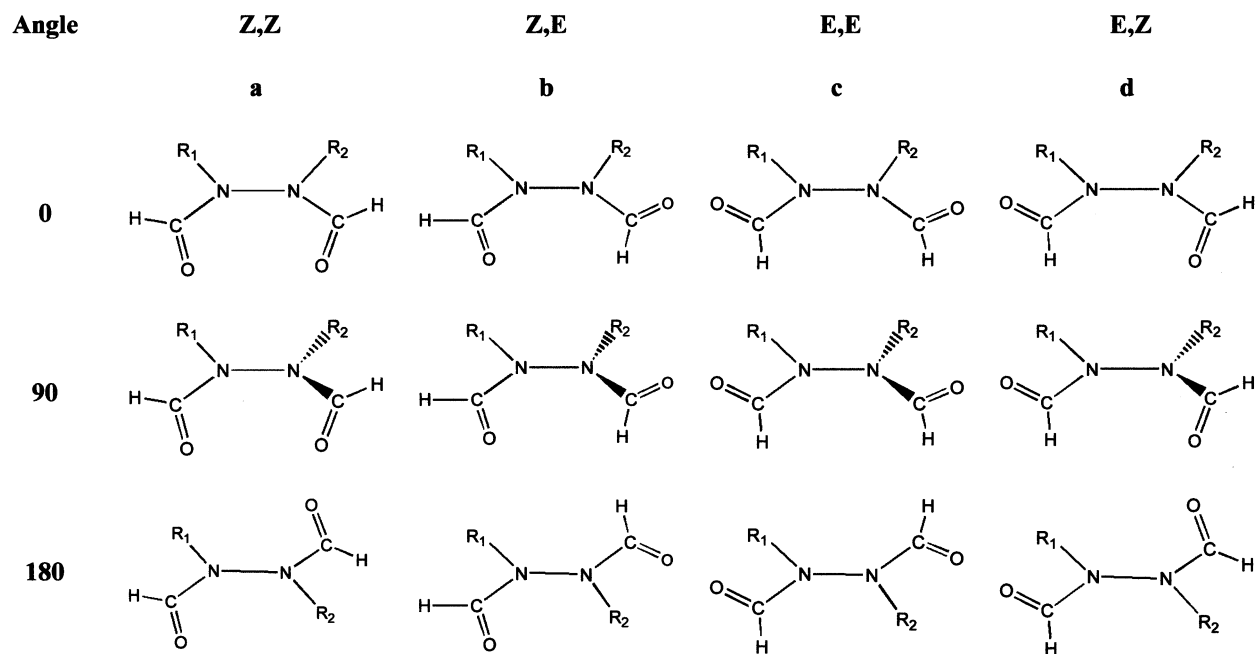
The relative bond rotational energy (RE) for MP2 and AMBER are written as follows:

$$\text{RE}_{\text{AMBER}^*}(\phi) = E_{\text{AMBER}^*}(\phi) - E_{\text{AMBER}^*}(\text{min})$$

$$\text{RE}_{\text{MP2}}(\phi) = E_{\text{MP2}}(\phi) - E_{\text{MP2}}(\text{min}) \quad (3)$$

The standard error between the two rotational barriers, which is to be minimized, can be written as

$$\text{SSQ} = \sum_{\{\phi\}} (\text{RE}_{\text{AMBER}^*} - \text{RE}_{\text{MP2}})^2 \quad (4)$$



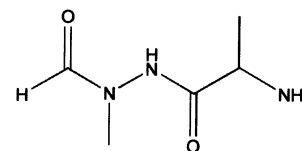
1a-c $R_1, R_2 = H$

2a-d $R_1 = \text{methyl}, R_2 = H$

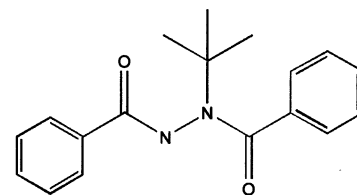
3a-c $R_1, R_2 = \text{methyl}$

4a-d $R_1 = t\text{-butyl}, R_2 = H$

5a-d $R_1 = t\text{-butyl}, R_2 = \text{methyl}$



6



7

Figure 1. Conformations for all four configurations of diformylhydrazine (**1**) and the critical dihedral angles (OHC-N-N CHO).

There are six possible X-N(sp²)-N(sp²)-Y interactions (parameters) that define the AMBER* torsional potential for different X and Y substituents (Table 3). For the sake of convenience, the equations relevant to the development of the torsional parameters { $V_1 \dots V_6$ } can be rearranged to the following form:

$$RE_{\text{AMBER}^*}(\phi) = RE_{\text{AMBER}'}(\phi) + V_1 f_1(\phi) + V_2 f_2(\phi) + V_3 f_3(\phi) + V_4 f_4(\phi) + V_5 f_5(\phi) + V_6 f_6(\phi) \quad (5)$$

where AMBER' is the AMBER* force field without the six torsional interactions above. A constrained optimization of the

standard error yields { $V_1 \dots V_6$ }. The final parameters extracted from the *amber.fld* file of the MacroModel package listing are given in Table 3 and Appendix 1. These parameters are qualified in the AMBER* parameter file so that they are only invoked when the CO-N-N-CO moiety is present.

RESULTS AND DISCUSSION

The calculated rotational barriers (Table 1) using the original AMBER* force field (as implemented in MacroModel) are compared with the MP2 calculations in Figures 2, 3 and 4. The average error for the rotational barriers using the original

Table 3. Modified AMBER* parameters for the CHO-N-N-CHO torsional potential

Torsional interaction	Symbol	Optimized value
1. $X-N(sp^2)-N(sp^2)-Y$	V_{original}	2.5
2. $OHC-N(sp^2)-N(sp^2)-CHO$	V_1	0.167
3. $H-N(sp^2)-N(sp^2)-CHO$	V_2	-2.600
4. $H-N(sp^2)-N(sp^2)-H$	V_3	1.253
5. $X-N(sp^2)-N(sp^2)-CHO$	V_4	-1.910
6. $X-N(sp^2)-N(sp^2)-H$	V_5	1.386
7. $X-N(sp^2)-N(sp^2)-Y$	V_6	-1.176

AMBER* parameters is 13.6 kcal/mol, with a maximum error of almost 26 kcal/mol (average errors were calculated using all 12 points on the potential surface, not just the critical points reported in the tables; see Figures 2–8). This clearly demonstrates the need for a new set of parameters to model the rotational barrier. Further inspection of Figures 2–4 shows that the original AMBER* parameters give rotational potential surfaces that are even qualitatively wrong. In general, the MP2 minima are predicted to be maxima by AMBER* and vice versa.

The newly optimized torsional parameters for **1–3** give calculated rotational barriers that are much improved over the original parameters. They result in calculated rotational barriers that have an average error of 1.6 kcal/mol and a maximum error of 6.2 kcal/mol relative to the MP2 calculations. In addition, the potential surfaces have the correct behavior at 0, 90 and 180°, i.e. the 90° rotamer is a minimum and the 0° and 180° rotamers are transition states. The minimum energy structures of all have dihedral angles between the nitrogen lone-pairs of approximately 90° in agreement with the ab initio results.^{14,31} The relative energies for the Z,E and E,E configurations of **1** with respect to the minimum energy configuration in the (Z,Z) configuration are 3.4 and 5.1 kcal/mol, respectively. These are higher than the 1.0 kcal/mol difference found for the optimized MP2 structures, but are an improvement over the original AMBER* values of 6.2 and 9.8 kcal/mol. The fitted parameters (Figure 3) yield an average error for the N-methyl derivative (**2**) of 1.2 kcal/mol and a maximum error of 5.7 kcal/mol, compared with 12.3 kcal/mol and 24.1 kcal/mol for the original AMBER* model. For the N,N'-dimethyl substituted diformylhydrazine (**3**), (Figure 4) the original AMBER* model had an average error of 14.5 kcal/mol and a maximum error of 28.9 kcal/mol. Both the average and maximum errors were drastically improved by the new parameter set to 2.1 kcal/mol and 5.2 kcal/mol, respectively. The relative energies of the critical points for hydrogen and methyl substituted diacylhydrazines (**1–3**) are given in Table 1. These results are also consistent with NMR studies that argue for nonplanar ground states and rotational barriers of 10–20 kcal/mol for substituted diacylhydrazines.^{14,32}

The N-*t*-butyl substituted diformylhydrazine (**4**), N-methyl-N'-*t*-butyl-diformylhydrazine (**5**), a model azadipeptide (**6**), and N-*t*-butyl-dibenzoylhydrazine (**7**) have been used to test the performance of these fitted parameters. These structures were chosen because they are larger and more structurally diverse. In addition, **6** is a good model for the N-N rotational barrier in an azapeptide and N-*t*-butyl-dibenzoylhydrazine (**7**)

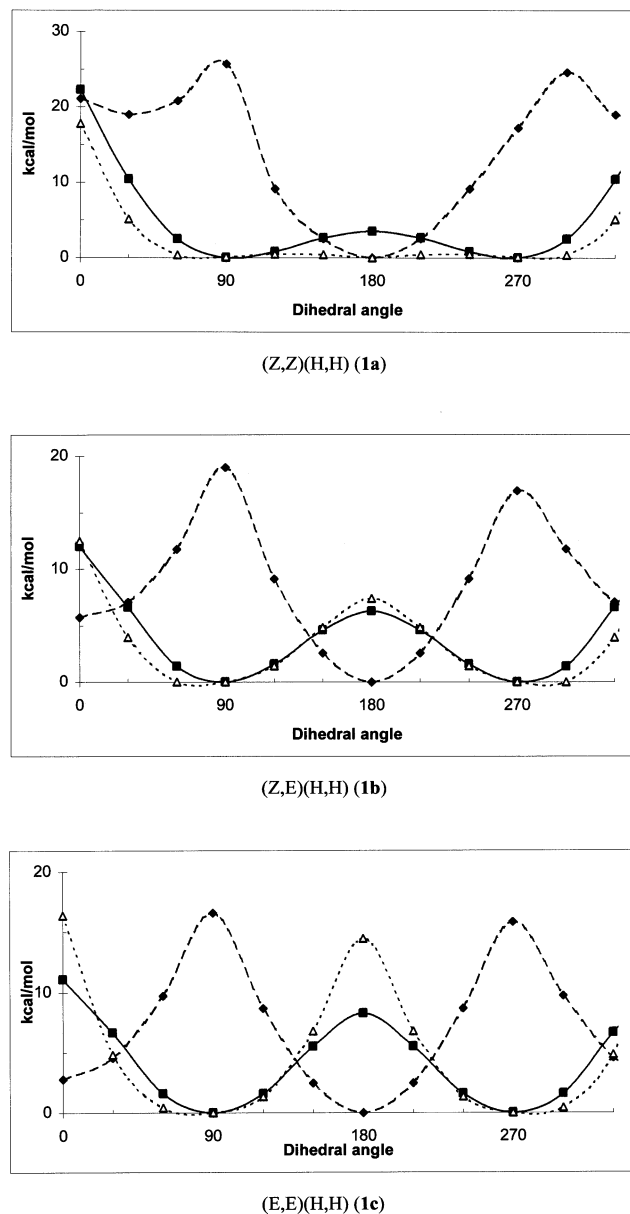
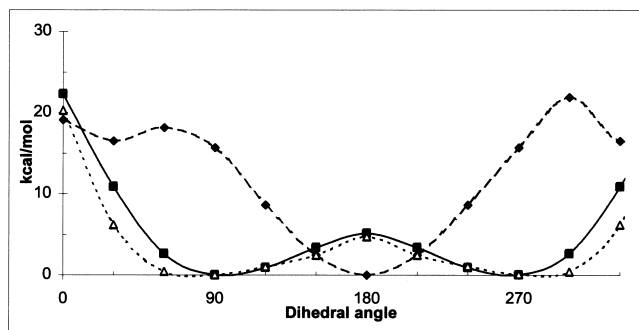
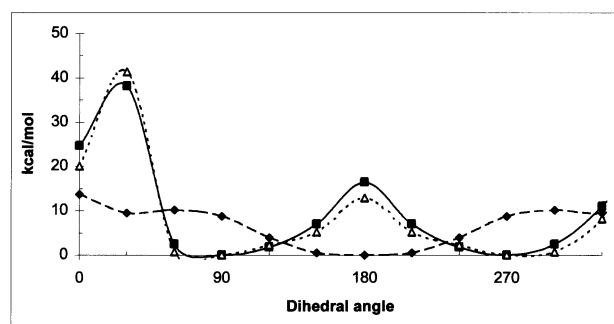


Figure 2. Original AMBER* (diamonds), MP2 single points (squares) and new AMBER* (open triangles) potential energy surfaces for rotation about the N-N bond of diformylhydrazine (**1a–1c**).

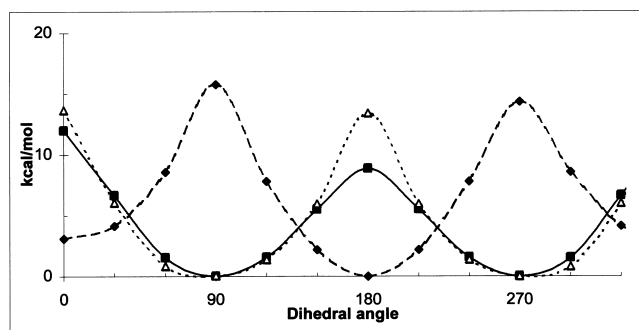
is a prototypical representative of the insecticidal class of nonsteroidal ecdysone agonists. The potential surfaces are summarized in Figures 5–8 and selected critical points are given in Table 4. The average errors compared to the MP2 calculations are 1.6 kcal/mol for **4** and 3.5 kcal/mol for **5**. The maximum errors are 5.9 kcal/mol and 9.9 kcal/mol, respectively. The errors for the N-methyl-N'-*t*-butyl-diformylhydrazine (**5**) are about 4 kcal/mol higher than for the other cases. The larger errors are attributable to conformations where the very bulky *t*-butyl group is forced to be gauche or eclipsed with another substituent. The potential energy surfaces for rotating about the N-N bond in dibenzoylhydrazine (**6**) and the model azadipeptide (**7**) are shown in Figures 7 and 8. The relative



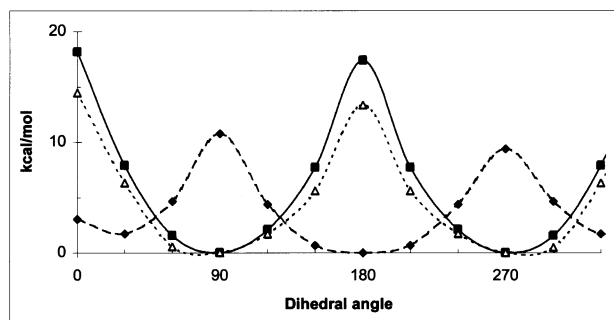
(Z,Z)(Me,H) (2a)



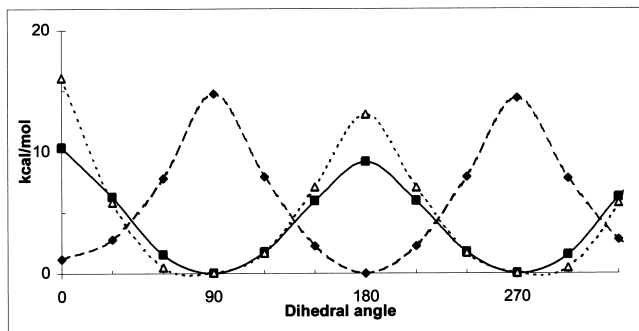
(Z,Z)(Me,Me)(3a)



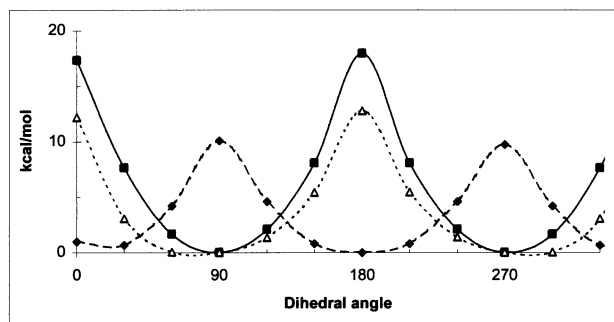
(Z,E)(Me,H) (2b)



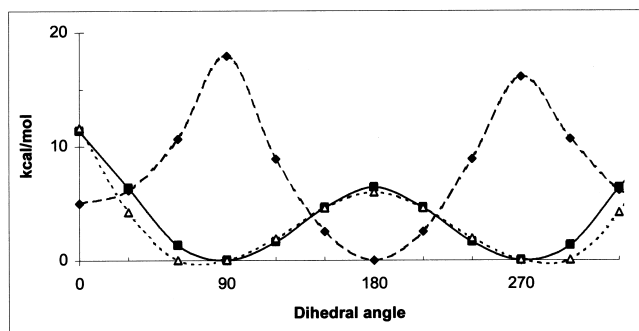
(Z,E)(Me,Me)(3b)



(E,E)(Me,H) (2c)



(E,E)(Me,Me)(3c)

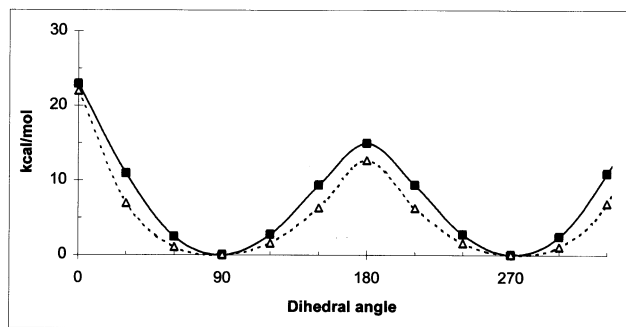


(E,Z)(Me,H) (2d)

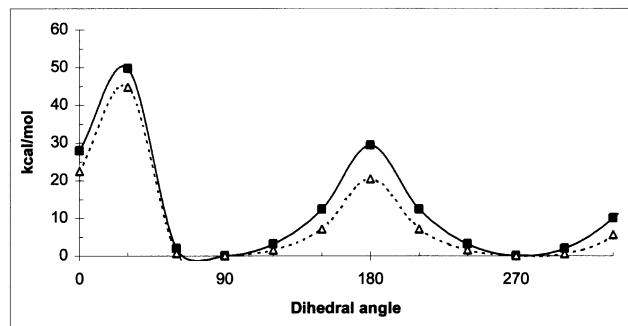
Figure 3. Original AMBER* (diamonds), MP2 single points (squares) and new AMBER* (open triangles) potential energy surfaces for rotation about the N-N bond of N-methyl-diformylhydrazine (2a–2d).

Figure 4. Original AMBER* (diamonds), MP2 single points (squares) and new AMBER* (open triangles) potential energy surfaces for rotation about the N-N bond of N,N'-dimethyl-diformylhydrazine (3a–3c).

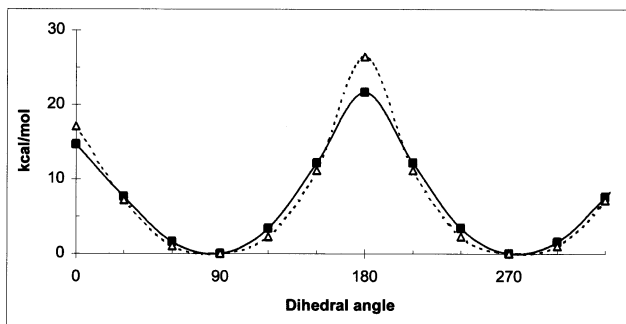
energies for rotation about the N-N bond in **6** and **7** are also given in Table 4. The rotational potentials for **6** and **7** are qualitatively consistent with the MP2 single point calculations. The maximum errors relative to MP2/6-31+G** are 4.8 kcal/mol and 9.7 kcal/mol and the average errors are 1.5 kcal/mol and 3.3 kcal/mol. As was true in structures **4** and **5**, the errors in the rotational barriers for **6** and **7** are driven up by the conformations where relatively bulky substituents are forced into a gauche or eclipsed relationship. For example, in the E,E configuration of **7** the barrier height (Figure 8) is severely overestimated by the modified AMBER* force field even though agreement with MP2 is quite good for the other configurations.



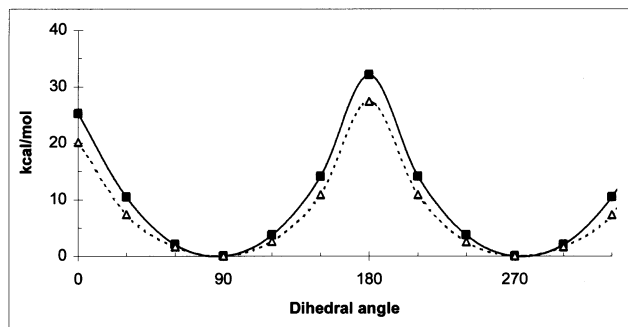
(Z,Z)-(t-Bu,H)(4a)



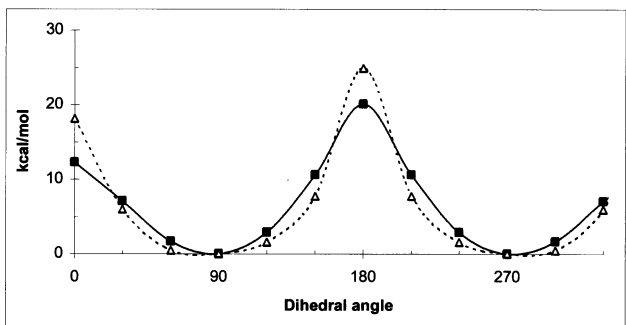
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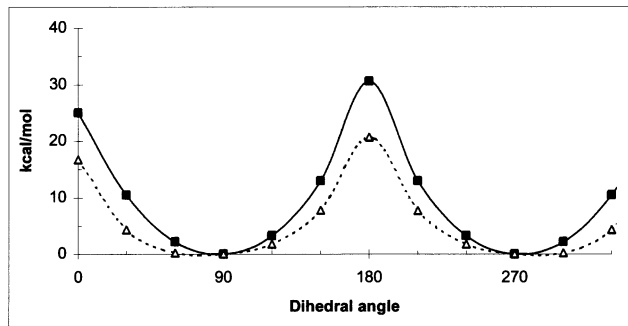
(Z,E)-(t-Bu,H)(4b)



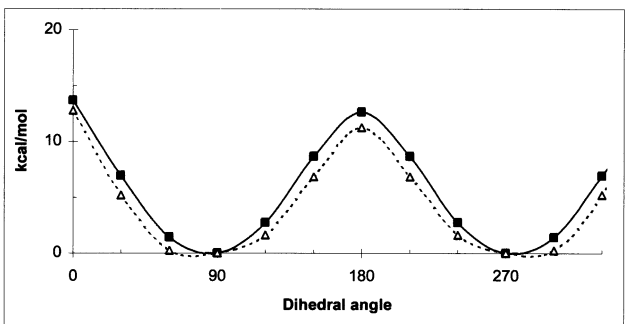
(Z,E)-(t-Bu,Me)(5b)



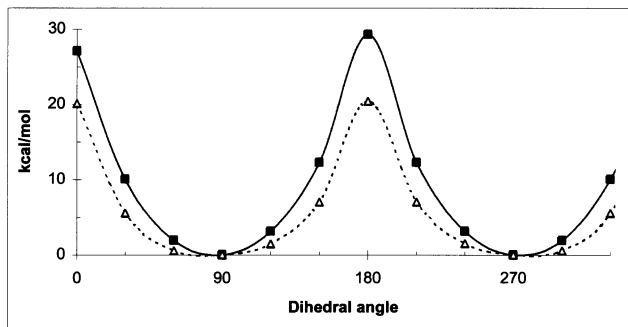
(E,E)-(t-Bu,H)(4c)



(E,E)-(t-Bu,Me)(5c)



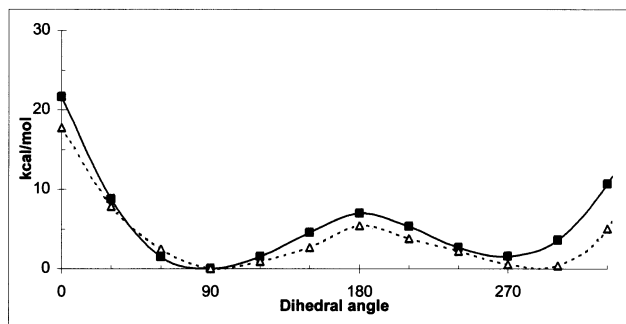
(E,Z)-(t-Bu,H)(4d)



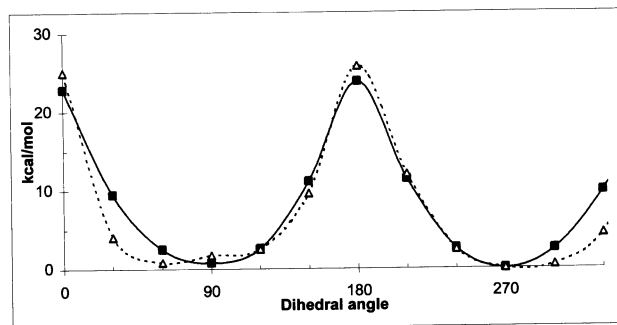
(E,Z)-(t-Bu,Me)(5d)

Figure 5. MP2 single points (open triangles) and new AMBER* (squares) potential energy surfaces for rotation about the N-N bond of N-t-butyl-diformylhydrazine (4a–4d).

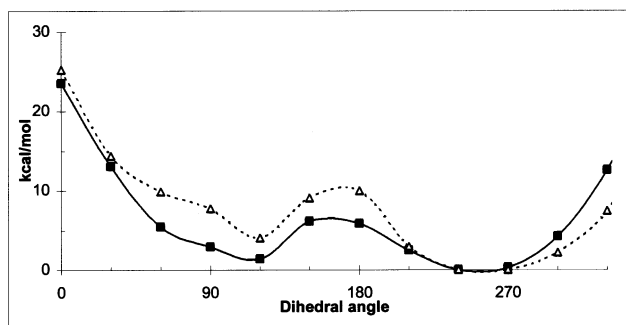
Figure 6. MP2 single points (open triangles) and new AMBER* (squares) potential energy surfaces for rotation about the N-N bond of N-methyl-N'-t-butyl-diformylhydrazine (5a–5d).



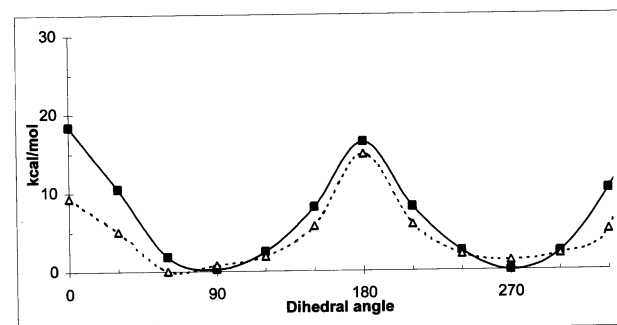
(Z,Z) 6a



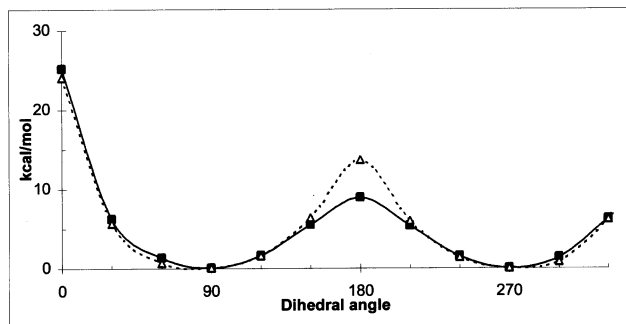
(Z,Z) 7a



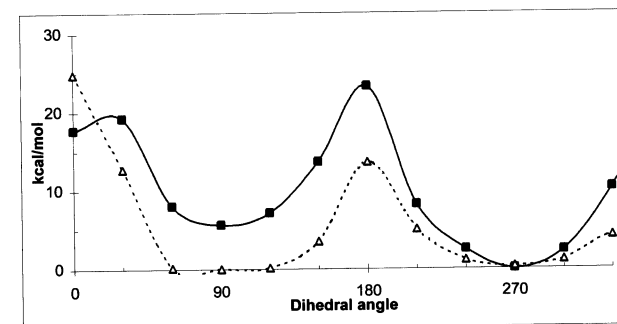
(Z,E) 6b



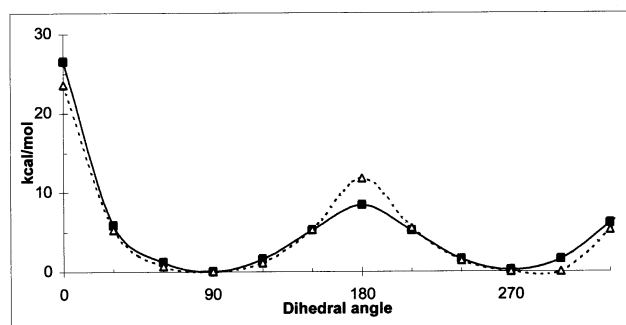
(Z,E) 7b



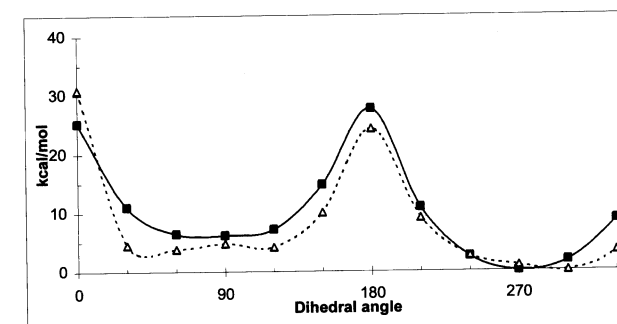
(E,E) 6c



(E,E) 7c



(E,Z) 6d



(E,Z) 7d

Figure 7. MP2 single points (open triangles) and new AMBER* (squares) potential energy surfaces for rotation about the N-N bond of the model azadipeptide (6a–6d).

Figure 8. MP2 single points (open triangles) and new AMBER* (squares) potential energy surfaces for rotation about the N-N bond of *N*-*t*-butyl-dibenzoylhydrazine (7a–7d).

Table 4. Selected relative rotational barriers for 4–7 in kcal/mol

Structure	Dihedral degree	AMBER* modified	MP2 single point	Error ^a	Structure	Dihedral degree	AMBER* modified	MP2 single point	Error ^a
4a (<i>tert</i> -Bu,H)	0	22.9	22.0	0.9	6a Z,Z	0	21.6	17.7	3.9
	90	0	0			90	0	0	
	180	15	12.7	2.3		180	7	5.4	1.6
4b Z,E	0	14.7	17.1	−2.4	6b Z,E	0	23.5	25.2	−1.7
	90	0	0			90	2.9	−4.8	
	180	21.7	26.4	−4.7		180	5.8	9.9	−4.1
4c E,E	0	12.3	18.2	−5.9	6c E,E	0	25.1	24.0	1.1
	90	0	0			90	0	0.1	−0.1
	180	20.1	24.9	−4.8		180	8.9	13.7	−4.8
4d E,Z	0	13.7	12.8	0.9	6d E,Z	0	26.5	23.5	3.0
	90	0	0			90	0	0	
	180	12.6	11.2	1.4		180	8.4	11.8	−3.4
5a (<i>tert</i> -Bu,Me)	0	27.9	22.4	5.5	7a Z,Z	0	22.8	25.0	−2.2
	90	0	0			90	0.8	1.7	−0.9
	180	29.3	20.4	8.9		180	23.8	25.7	−1.9
5b Z,E	0	25.2	20.2	5.0	7b Z,E	0	18.4	9.3	9.1
	90	0	0			90	0.2	0.8	−0.6
	180	32	27.4	4.6		180	16.4	14.9	1.5
5c E,E	0	25	16.7	8.3	7c E,E	0	17.7	24.8	−7.1
	90	0	0			90	5.6	0	5.6
	180	30.6	20.7	9.9		180	23.3	13.6	9.7
5d E,Z	0	27.1	20.1	7.0	7d E,Z	0	25.2	30.9	−5.7
	90	0	0			90	6.1	4.8	1.3
	180	29.3	20.4	8.9		180	27.6	24.2	3.4

RMS error^b 5.0
 unsign.avg.: 4.2

^aError relative to the MP2 single point energies in kcal/mol.

^bError for both columns neglecting the minimum energy conformations. Errors are smaller when all 12 points on the potential surfaces are considered; see text.

CONCLUSION

We have developed a modified set of AMBER* N-N torsional parameters for diacylhydrazines. These new AMBER* parameters give rotational barriers that are in good agreement with ab initio MP2/6-31+G** energies.

APPENDIX 1

Parameters extracted from the modified amber.fld file in MacroModel. These parameters should be inserted before the "00 * N2 * N2 * 00" entry in the torsional interaction section.

```

4 C2 * N2 - N2 * C2 0.0000 0.1670 0.0000 0200 0000 0000
  0200 A 3 OHC-N2-N2-CHO
4 C2 * N2 - N2 * HO 0.0000 -2.6000 0.0000 0200 0000
  0200 0000 A 3 OHC-N2-N2-H
4 HO * N2 - N2 * HO 0.0000 1.2530 0.0000 0000 C200 C200
  0000 A 3 H-N2-N2-H
4 C2 * N2 - N2 * 00 0.0000 -1.9100 0.0000 0200 0000 C200
  0000 A 3 OHC-N2-N2-X
4 HO * N2 - N2 * 00 0.0000 1.3860 0.0000 0000 C200 C200
  0000 A 3 H-N2-N2-X

```

```

4 00 * N2 - N2 * 00 0.0000 -1.17660 0.0000 0000 C200
  C200 0000 A 3 X-N2-N2-X

```

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