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Ab Initio and Molecular Mechanics Calculations of Various Substituted Ureas – Rotational Barriers and a New Parametrization for Ureas

Thomas Strassner [1]

Institut für Organische Chemie, Universität Erlangen-Nürnberg, Henkestr. 42, D – 91054 Erlangen, Germany
(strasner@organik.uni-erlangen.de)

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Abstract

High-level *ab initio* calculations have been performed on urea, methylurea, tetramethylurea and three isomers of dimethylurea to obtain accurate rotational barriers. Results of MP2(fc)/6-31 G(d) calculations are compared to those with lower basis sets and semiempirical calculations. The MM2(87) force field has been parameterized.

Keywords: MM2, parametrization, rotational barrier, urea, *ab initio*

Introduction

Today molecular modeling is an important tool for interdisciplinary research. Different methods are applied, depending on the size of the molecules. Though the computational power is still increasing, it is not feasible to study larger systems with *ab initio* quantum-chemical methods. The applicability of *ab initio* calculations increased due to the development of new supercomputers and the accuracy of *ab initio* calculations depends only on the choosen level, but still they are only useful for model compounds. Semiempirical calculations can deal with larger molecules of up to 500 atoms, but to study natural compounds with several possible conformations they are also not useful.

Force field methods enable scientists to calculate large structures with up to 10.000 atoms, but the quality of force field calculations depends on the availability of reliable force field parameters which are consistent with earlier parameter sets to ensure that the results of previous calculations can be compared with actual computations.

Since Wöhlers synthesis in 1828 urea is known as the starting point of organic chemistry. Its structural unit can be found in molecules which are essential for many natural processes. Moreover, the R_2N-CO-NR_2 unit is a basic constituent of various enzymes, nucleotides and of interesting compounds with possible pharmazeutical applications. Recently published papers including a structure of a HIV-inhibitor compound show the interest in this structural unit [2]. You can find the -NH-CO-NH- fragment in many natural compounds (e.g. barbiturates, vitamine B_{13}, purines and pyrimidines) [3].

To study biological important systems force field calculations are necessary because of the size of the molecules. The importance and acceptance of molecular modelling increases, due to the efficiency and reliability of the results. These techniques are based on empirical force-field methods, which are parametrized for a wide variety of substances. Usually all parameters are developed independently, but the existing parametrization for ureas by Bowen et al. [4] changes the parameters for amides, so the consistency will be lost when the results of previous calculations of amides are compared to actual ones.

Ureas have been studied extensively in various ways, theoretically as well as experimentally. Especially the interaction between urea and water or the protein denaturation was of considerable interest [5]. Ureas are able to interact with a wide variety of compounds, they can form hydrogen bonds with electron acceptors and donators and they are known to

Table 1. *Mean values of compound classes G - M (see figure 2). Maximum deviation is given in brackets.*

	G	H	I	K	M
NC (Å)	1.37 (0.05)	1.36 (0.07)	1.37 (0.03)	1.36 (0.06)	1.36 (0.04)
CO(Å)	1.22 (0.03)	1.23 (0.03)	1.21 (0.02)	1.22 (0.03)	1.23 (0.03)
NCN (°)	107.2 (1.1)	107.7 (2.4)	116.7 (2.8)	116.5 (2.3)	113.8 (4.9)
NCNX (°)	4.1 (12.5)	4.6 (13.8)	2.9 (10.3)	3.5 (10.7)	6.8 (11.4)

form cocrystals [6]. The interactions of ureas with other molecules were studied by X-ray-analysis [7] and the question whether urea is planar or not received a lot of attention during the last years. This study cannot contribute to a discussion where results of calculations on much higher levels of theory are discussed. The intention is the development of a consistent set of reliable parameters from thorough *ab initio* studies of rotational barriers of different substituted ureas. The semi-empirical rotational barriers of ureas are well studied [8] and will be compared to the results of high-level *ab initio* calculations.

To build a parameter set for ureas the accuracy of semi-empirical calculations was not sufficient. Exact *ab initio* data concerning the rotational barriers of different substituted and unsubstituted ureas were necessary. The presented study also gave insight into the rotational barriers of different ureas, which are shown in figure 1.

Computational Details

All calculations were carried out using the GAUSSIAN 92 [9] and GAUSSIAN 94 [10] program. The standard basis sets 3-21G and 6-31G* were used in all calculations. Correlation energy was considered by Møeller-Plesset perturbation theory up to the second order including all innermost and outermost virtual orbitals. The MP2 calculations were done with frozen core. The geometries were completely optimized with a constraint on the dihedral angle ρ_1 (rotation of the NR_1R_2-group). All calculations were performed in 30 degree increments between 0 and 330 degrees, only the MP2-calculations were done from 0 to 180 degrees while the second barrier was calculated at 270 degrees.

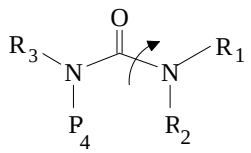
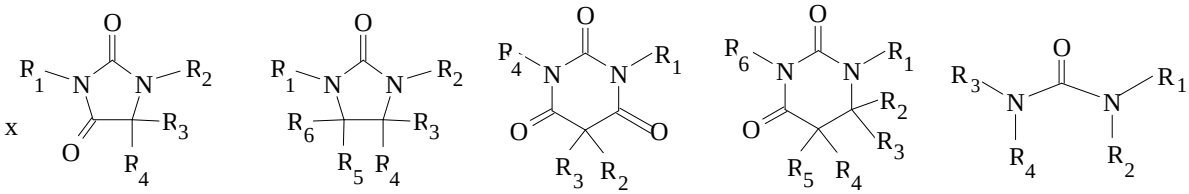


Figure 1. *Studied ureas A – F.*
A: $R_1=R_2=R_3=R_4= H$
B: $R_1=CH_3$, $R_2=R_3=R_4= H$
C: $R_1=R_4=CH_3$, $R_2=R_3= H$
D: $R_1=R_4=H$, $R_2=R_3= CH_3$
E: $R_1=R_2=CH_3$, $R_3=R_4= H$
F: $R_1=R_2=R_3=R_4= CH_3$

MM2 - parametrization

MM2(87) [11] with the newest parameter set was used for the parametrization. This set was announced as the final parameter set of MM2. The data of the *ab initio* rotational barriers were used to calibrate the parameters. A previous work [4] concerning the parametrization of urea compounds did not take into account the problem you encounter in the sense of consistency, if you change the values of angles and dihedral angles incorporated in amide units. This problem was



G (19) **H** (20) **I** (36) **K** (20) **L** (15)

Figure 2. *Compound classes containing a -N-CO-N- unit*

Table 2. *Energy differences of rotational isomers. All energies are given relative to the 0° torsion (3-21G: -222.73683; 6-31G*: -223.98421; MP2/6-31G*: -224.60680).*

Urea			
A	**3-21G**	**6-31G***	**MP2/6-31G***
angle	*kcal/mol*	*kcal/mol*	*kcal/mol*
0°	0	0	0
30°	+ 2.58	+ 5.17	+ 5.13
60°	+ 8.23	+ 12.07	+ 11.12
90°	+ 10.92	+ 15.50	+ 14.58
120°	+ 8.23	+ 12.07	+ 11.12
150°	+ 2.58	+ 1.32	+ 0.89
180°	0	+ 0.001	+ 1.32
210°	+ 2.58	+ 1.32	-
240°	+ 8.23	+ 6.21	-
270°	+ 10.92	+ 8.69	+ 7.64
300°	+ 8,.3	+ 6.21	-
330°	+ 2.58	+ 1.32	-
360°	0	0	0

Table 3. *Energy differences of rotational isomers. All energies are given relative to the 0° torsion (3-21G: -261.55084; 6-31G*: -263.01335; MP2/6-31G*: -263.76561)*

Methylurea			
B	3-21G	6-31G*	MP2/6-31G*
angle	*kcal/mol*	*kcal/mol*	*kcal/mol*
0°	0	0	0
30°	+ 3.18	+ 1.90	+ 5.26
60°	+ 9.39	+ 12.87	+ 12.08
90°	+ 17.88	+ 16.82	+ 15.74
120°	+ 9.70	+ 13.96	+ 12.90
150°	+ 4.74	+ 3.38	+ 2.84
180°	+ 1.72	+ 1.52	+ 1.33
210°	+ 4.75	+ 3.37	-
240°	+ 9.70	+ 7.73	-
270°	+ 12.23	+ 10.21	+ 8.96
300°	+ 9.39	+ 6.99	-
330°	+ 3.16	+ 1.90	-
360°	0.00	0.00	0

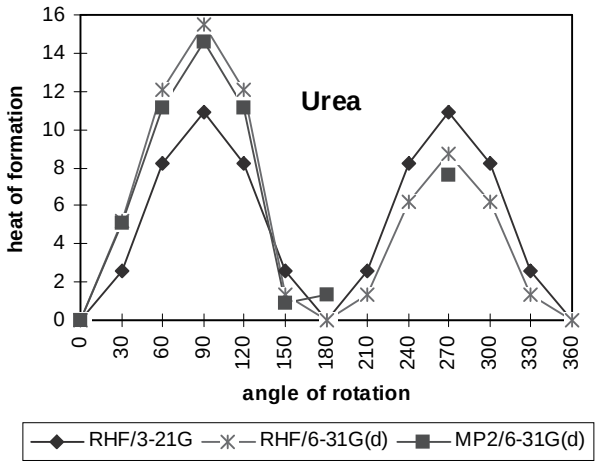


Figure 3. *Rotational barriers of urea*

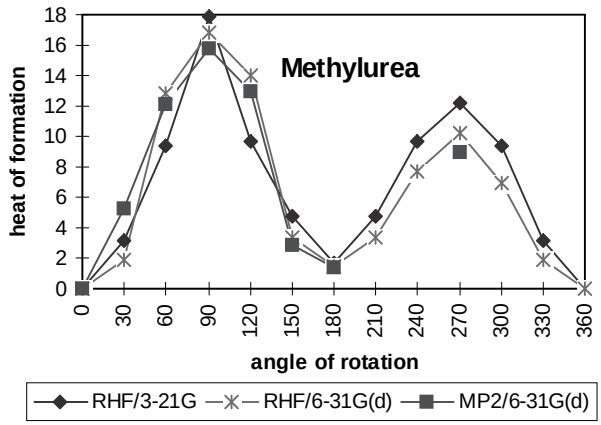


Figure 4. *Rotational barriers of methylurea.*

Table 4. *Energy differences of rotational isomers. All energies are given relative to the 0° torsion (3-21G: -300.36468; 6-31G*: -302.04207; MP2/6-31G*: -302.92411)*

Dimethylurea Type C			
C	**3-21G**	**6-31G***	**MP2/6-31G***
angle	*kcal/mol*	*kcal/mol*	*kcal/mol*
0°	+ 0.00	+ 0.00	+ 0.00
30°	+ 3.18	+ 1.65	+ 1.19
60°	+ 9.15	+ 12.06	+ 11.05
90°	+ 11.97	+ 15.95	+ 14.55
120°	+ 9.45	+ 13.23	+ 11.85
150°	+ 4.73	+ 3.09	+ 2.40
180°	+ 1.75	+ 1.46	+ 1.72
210°	+ 5.11	+ 3.09	-
240°	+ 9.75	+ 6.83	-
270°	+ 11.98	+ 9.04	+ 7.16
300°	+ 9.25	+ 6.79	-
330°	+ 3.18	+ 1.65	-
360°	0.00	0.00	0.000

Table 5. *Energy differences of rotational isomers. All energies are given relative to the 0° torsion (3-21G: -300.34852; 6-31G*: -302.03034; MP2/6-31G*: -302.91451)*

Dimethylurea Type D			
D	**3-21G**	**6-31G***	**MP2/6-31G***
angle	*kcal/mol*	*kcal/mol*	*kcal/mol*
0°	+ 8.39	+ 5.91	+ 4.85
30°	+ 6.87	+ 4.88	+ 3.64
60°	+ 10.04	+ 9.00	+ 6.58
90°	+ 12.47	+ 18.21	+ 16.81
120°	+ 9.50	+ 8.03	+ 6.89
150°	+ 3.11	+ 2.23	+ 1.78
180°	+ 0.00	0.0	0.0
210°	+ 3.11	+ 2.23	-
240°	+ 9.50	+ 8.03	-
270°	+ 12.47	+ 10.58	+ 8.79
300°	+ 10.04	+ 8.12	-
330°	+ 6.87	+ 4.88	-
360°	+ 8.39	+ 5.91	+ 4.85

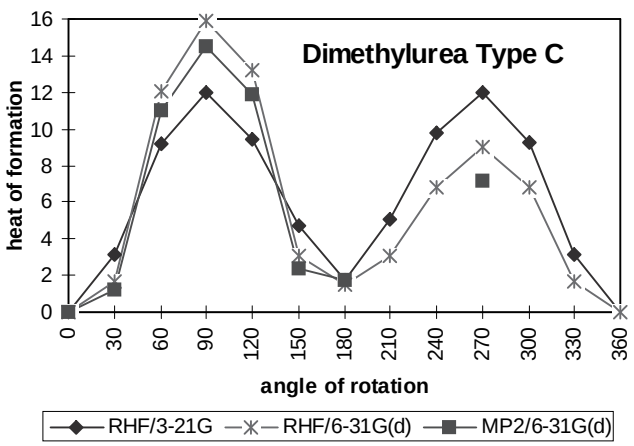


Figure 5. *Rotational barriers of dimethylurea type C*

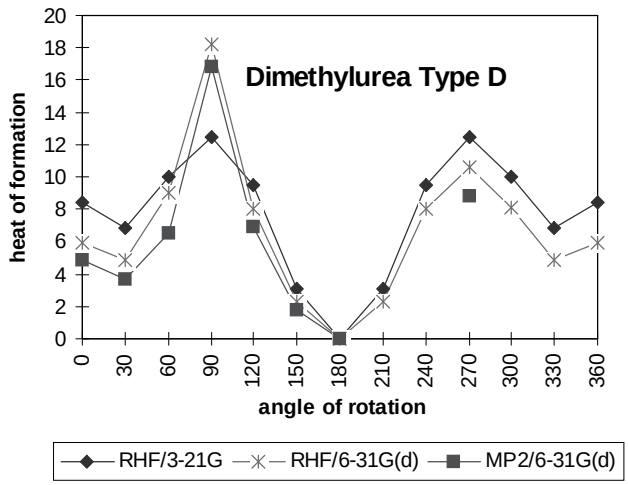


Figure 6. *Rotational barriers of dimethylurea type D*

Table 6. *Energy differences of rotational isomers. All energies are given relative to the 0° torsion (3-21G: -300.36151; 6-31G*: -302.03778; MP2/6-31G*: -302.92363)*

Dimethylurea Type E

E	**3-21G**	**6-31G***	**MP2/6-31G***
angle	*kcal/mol*	*kcal/mol*	*kcal/mol*
0°	+ 0.001	+ 0.01	- 0.0003
30°	+ 2.43	+ 1.18	+ 0.88
60°	+ 7.1	+ 10.71	+ 10.21
90°	+ 14.81	+ 13.74	+ 13.05
120°	+ 7.10	+ 10.71	+ 10.21
150°	+ 2.43	+ 1.18	+ 0.88
180°	+ 0.00	0	0.00
210°	+ 2.43	+1.18	-
240°	+ 7.1	+ 5.40	-
270°	+ 9.66	+ 7.61	+ 6.69
300°	+ 7.1	+ 5.40	-
330°	+ 2.43	+ 1.18	-
360°	+ 0.001	+ 0.01	- 0.0003

Table 7. *Energy differences of rotational isomers. All energies are given relative to the 0° torsion (3-21G: -377.97596; 6-31G*: -380.08382; MP2/6-31G*: -381.23600)*

Tertramethylurea

F	**3-21G**	**6-31G***	**MP2/6-31G***
angle	*kcal/mol*	*kcal/mol*	*kcal/mol*
0°	+ 2.52	+ 2.44	+ 2.05
30°	+ 0.000	+ 0.000	+ 0.000
60 °	+ 2.74	+ 2.68	+ 2.22
90°	+ 4.93	+ 4.75	+3.77
120°	+ 2,74	+ 2.68	+2.22
150°	- 0,001	- 0.001	+0.0001
180°	+ 2.52	+ 2.44	+ 2.05
210°	-0.001	-0.001	-
240°	+ 2.74	+ 2.68	-
270°	+ 4.93	+ 4.75	+ 3.77
300°	+ 2.74	+ 2.68	-
330°	- 0.001	- 0.0008	-
360°	+ 2.52	+ 2.439	+ 2.05

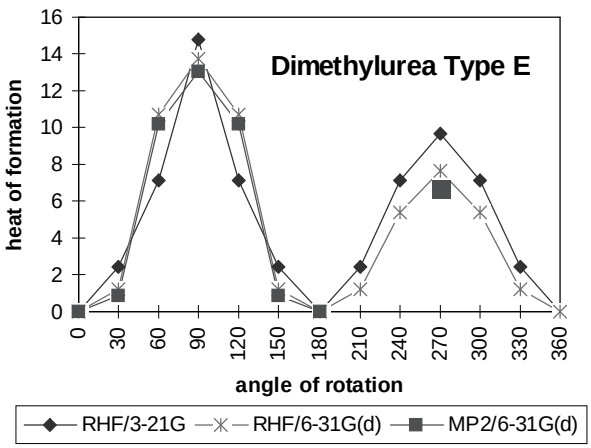


Figure 7. *Rotational barriers of dimethylurea type E*

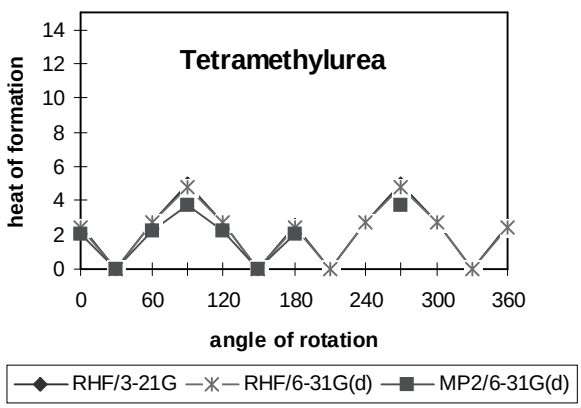


Figure 8. *Rotational barriers of tetramethylurea.*

Table 8. *Barrier heights calculated with different hamiltonians and basis sets compared to experimental values*

	A	B	C	D	E	F
RHF/3-21G	10.9	12.2	12.0	12.5	9.7	4.9
RHF/6-31G(d)	8.7	10.2	9.0	10.6	7.6	4.8
MP2(fc)/6-31G(d)	7.6	9.0	7.2	8.8	6.7	3.8
AM1	4.8	4.1	5.0	4.0	3.8	1.6
MNDO	3.2	2.9	2.1	1.8	1.6	0.8
PM3	3.4	2.5	4.6	2.4	1.0	2.0
Experiment	11.3	13.2	-	-	10.7	6.3

solved, the original MM2-parameters for amides are used and only parameters of urea units are changed. The new parameter set for urea compounds was compared to the structural information received by analyzing several structural classes (figure 2) containing urea units, which have been choosen from about 300 X-ray-structures. Many of those structures are ureas complexed by different metals, eg. Al [12], Ba [13], Co [14], Cd [15], Cu [16], Er [17], Eu [18], Fe [19], Hg [20], Ir [21], In [22], K [23], Li [24], Mg [25], Mn [26], Mo [27], Pt [28], Rb [29], Ru [30], U[31], or charged systems [32]. Those molecules often show unusual binding situations and have not been considered. The numbers in brackets give the number of considered structures, table 1 shows typical bond length, angles and dihedral angles.

Rotational barriers

Tables 2 to 7 and figures 3 to 8, respectively, show the rotational barriers of urea, methylurea, dimethylurea type C, D and E and tetramethylurea.

Comparison of *ab initio* calculations, semiempirical calculations and experimental data

Unfortunately no gas phase NMR data of the rotational barriers are available, but most of the barriers measured in solution are known. Their values are : Urea is 11.3 kcal/mol [33], methylurea for the rotation about the $NH(CH_3)$- bond is 13.2 kcal/mol [34] with a difference of 12.3 kcal/mol between the cis- and trans-isomers. Dimethylurea of type E is 10.7 kcal/mol [34] and tetramethylurea is 6.3 kcal/mol [35]. The dimethylureas type C and D were also measured, but the only result has been that one isomer is dominant. No value for the rotational barrier was found.

Obviously there is only a small influence of the basis set. The shape of the barriers is very similar, only their height is slightly different. There are always two barriers (except tetramethylurea F) for all molecules due to the pyrimidalization of the nitrogen. The lower value of the two barriers has to be considered as rotational barrier and corre-

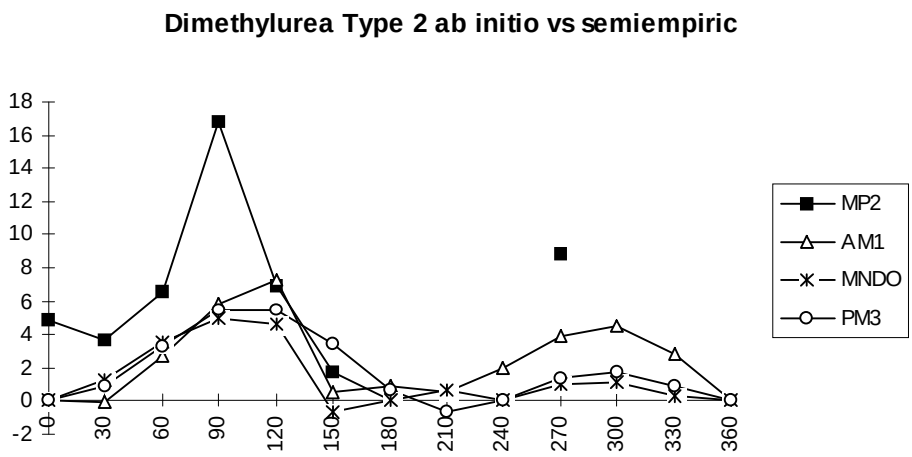


Figure 9. *Barrier of compound D calculated with MP2(fc)/6-31G(d) and AM1, MNDO, PM3*

Table 9. *Parameter set of the original MM2-code compared to the new parameter set*

	MM2			new set		
atomtype	V_1	V_2	V_3	V_1	V_2	V_3
9 3 9 3	0.8	1.3	0.0	0.8	2.0	0.0
7 3 9 3	0.6	1.3	0.0	0.0	0.0	0.0
9 3 9 28	0.0	1.0	0.0	1.0	1.0	0.0
9 3 9 1	0.0	0.0	0.01	3.0	6.0	0.0
9 1 1 9	0.0	0.0	-0.5	2.0	0.3	0.1
atomtype	k_B	angle		k_B	angle	
2 1 9	0.5	109.8		0.82	109.8	
2 2 9	0.5	118.0		0.52	120.0	
2 9 2	0.4	107.0		0.56	110.0	
3 9 2	0.6	115.0		0.6	115.0	
3 9 3	0.5	125.0		0.65	120.0	
9 3 9	0.5	120.0		1.0	110.0	
3 9 28	0.42	119.0		0.6	119.0	
0 9 28	0.010			0.8		

sponds always to the 270 degree structure, where the lone pair of the nitrogen is pointing away from the carbonyl oxygen. The 3-21G basis set calculates higher barriers than the 6-31G(d) basis set, whereas the inclusion of correlation with the MP2-calculations lowers the barriers (see table 8).

All rotational barriers were recalculated with AM1, MNDO and PM3. The results are shown in table 8. It is known for a long time that semiempirical methods have problems reproducing experimental values of rotational barriers. It is obvious that in this case of different substituted ureas this is especially true. All three semiempirical hamiltonians are unable to calculate values which are at least close to the experimental ones. Figure 9 shows the differences between the MP2-calculation, which gives the lowest barriers of all *ab initio*-methods and the barriers calculated with all three semiempirical hamiltonians.

Parameters

For a better comparison of the changes the original MM2-parameters are given together with the new set in table 9.

Comparison of rotational profiles calculated with the new parameter set / *ab inito* (MP2(fc)/6-31G(d)

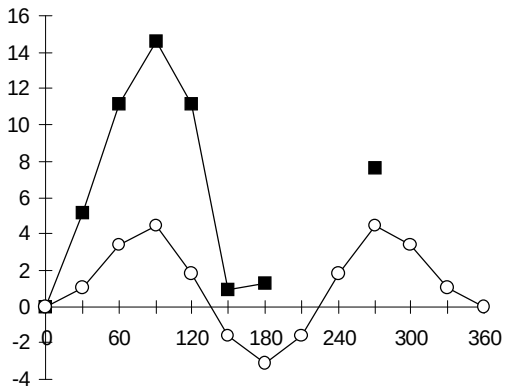
Figure 10 shows the result of the comparison of the rotational barriers calculated with the new MM2-parameter set and the *ab initio* calculations.

	X-ray-data		new parameter set	
	NCN	NCNX	NCN	NCNX
G	107.2 (1.1)	4.1 (12.5)	106.1 (0.3)	0.03 (0.1)
H	107.7 (2.4)	4.6 (13.8)	106.8 (0.2)	0.7 (2.0)
I	116.7 (2.8)	2.9 (10.3)	115.8 (1.1)	9.1 (15.6)
K	116.5 (2.3)	3.5 (10.7)	115.8 (0.7)	5.0 (9.3)
L	113.8 (4.9)	6.8 (11.4)	116.7 (5.7)	3.5 (26)

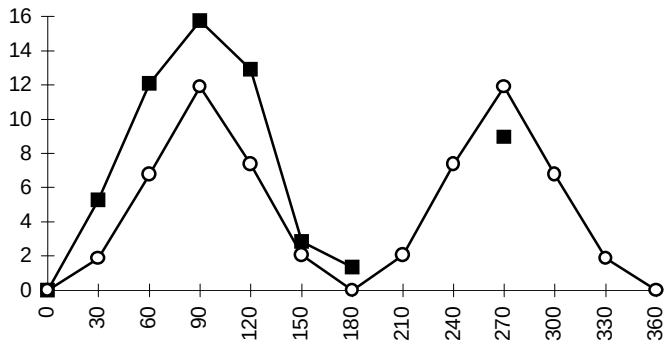
Table 10. *Comparison of the angles between both nitrogens and the central carbon atom as well as the corresponding dihedral angles. The numbers in brackets mention the maximum deviation which was observed.*

	N-C	C-O	N-C-N	N-C-O
RHF/6-31G(d) [36]	1.373	1.197	114.0	123.0
MP2/6-31G(d) [37]	1.389	1.225	113.0	123.5
6-31G(d,p) [37]	1.388	1.224	113.0	123.523
MM2 (parameters from (5))	1.374	1.219	116.9	121.5
MM2 (new parameter set)	1.373	1.217	112.8	123.6

Table 11a. *Comparison of MM2-results with ab initio - calculations for urea.*



Compound A



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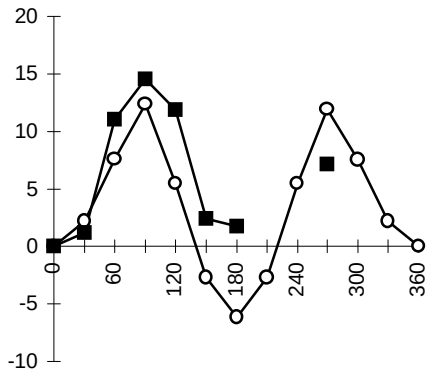
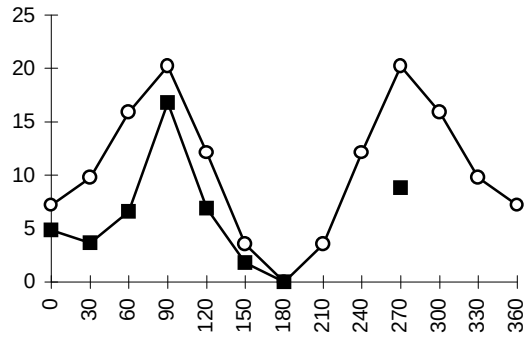
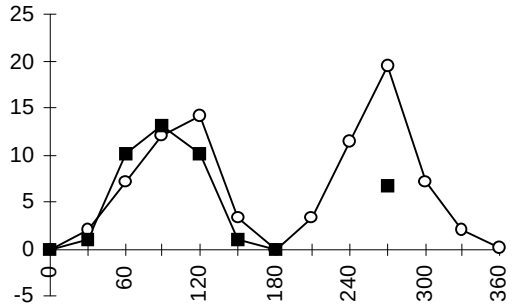


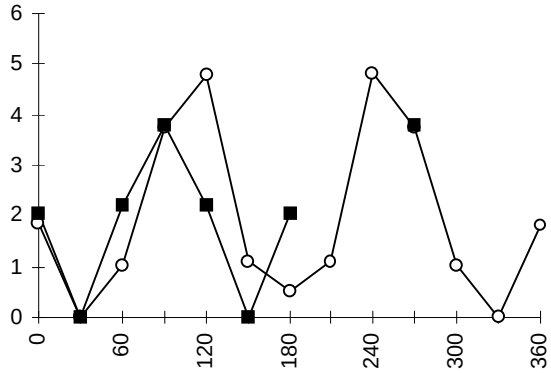
Compound C



Compound D



Compound E



Compound F

Figure 10. *Rotational barriers calculated with the new MM2-parameter set (--o--) compared with ab initio MP2(fc)/6-31G(d) calculations (--■--). The x-axis gives the angle of rotation around the bond shown in figure 1, the y-axis energies in kcal/mol.*

Table 11b. *Comparison of MM2-results with ab initio - calculations for tetramethylurea.*

	C-N	N-C(O)	C-O	N-C-N	C-N-C-O	C-N-C-N
RHF/6-31G(d)	1.45	1.38	1.21	116.3	6.7	173.4
MM2 (parameters from (5)	1.46	1.4	1.23	124.7	-8.5	171.5
MM2 (new set)	1.46	1.4	1.23	117.9	10.9	169.1

Comparison of Xray-data with calculated structural parameters

As mentioned before several X-ray structures (G -L, see figure 2) were used for comparison. The results are shown in table 10. All calculated values are within the deviation of the Xray structures. The calculated bond length are in good agreement with experimental data.

Comparison with several examples

The parameters were used to calculate several compounds, where ab inito calculations were published or available. The results are shown in table 10 and 11. Again the force field calculations are in good agreement.

Conclusion

The MM2 force field was reparametrized for the R_2N-CO-NR_2-unit through fitting of *ab initio* and X-ray data. Molecular geometries and rotational barriers were calculated on different levels of theory. With the new parameter set MM2 was able to reproduce the results of *ab initio* calculations als well as the Xray data of several compound classes. *Ab initio* calculations of the rotational barriers of urea, methylurea, different dimethylureas and tetramethylurea allow a comparison of the influence of the basis set on the rotational barrier. The RHF/3-21G, RHF/6-31G(d) and the MP2(fc)/6-31G(d) basis sets have been employed.

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1. Present address: Institut für Organische Chemie, Technische Universität Dresden, Mommsenstr. 13, D – 01069 Dresden, Germany. Tel.: (0351) 463-3211, Fax: (0351) 463-7030
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