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AMBER FORCE FIELD PARAMETERS FOR THE TRIMETHYLANILINIUM CATION

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Abstract: The AMBER force field was extended to include the trimethylanilinium cation. *Ab initio* and electrostatic fitting calculations were used to derive new AMBER parameters to describe the nitrogen-aryl carbon and nitrogen-united methyl bonds of the trimethylanilinium cation. These parameters should be useful in modeling synthetic macrocyclic hydrophobic cavities which incorporate the anilinium cation as a structural element.

The anilinium cation is a favored structural element of many synthetic macrocyclic hydrophobic cavities as it imparts water solubility and structural rigidity on the cavity (see Figure I).[1-2] As part of our continuing interest in hydrophobic binding,[3] we wished to model these compounds using molecular mechanics techniques. However, the anilinium cation is not parameterized in the common force field packages. In particular, parameters for bonds between quaternary nitrogen atoms and aryl carbon atoms are currently absent. Accordingly, we have used *ab initio* and electrostatic fitting calculations to define AMBER force field parameters for the trimethylanilinium cation and wish to report these herein. Calculated *ab initio* structures were found to be in good agreement with published x-ray crystallographic data.[4] Interestingly, semi-empirically derived structures were also very similar to the *ab initio* generated structures.

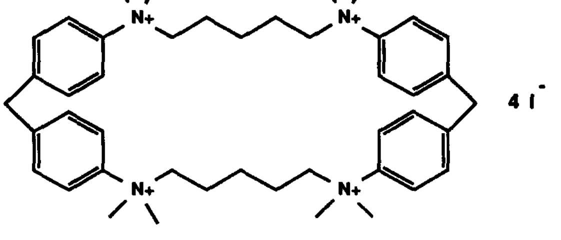

Figure I: A typical synthetic macrocyclic hydrophobic cavity which incorporates the trimethylanilinium cation.

The AMBER force field[5] as implemented in MacroModel 3.0[6] was employed in this study. Most calculations were carried out on a Convex 210 mainframe and on a network consisting of 5 Digital Microvax III workstations governed by VMS 5.1. The calculations with GAUSSIAN 90[7] were carried out on the Pittsburgh Cray (CRAY-YMP).

Due to its size, the trimethylanilinium cation was initially geometry-optimized using the AM-1 Hamiltonian available in AMPAC 1.0.[8] All N-C(sp^3) bonds were constrained to be of equal length and C_{2v} symmetry was assumed for the aromatic ring. The minimum energy structure featured one methyl group in the plane of the aromatic ring. A saddle point calculation found the energy maxima of the rotation around the N-C(sp^2) single bond (see Figure II). Comparison of the AM-1 minimum and maximum energy structures for this rotation yielded a torsional barrier of only 0.4 kcal/mol.

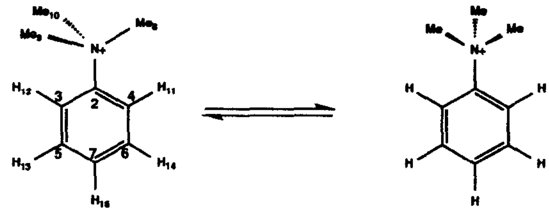

Figure II: Minimum energy (left) and saddle point (right) structures for the trimethylanilinium cation illustrate the three-fold rotational barrier (the numbering scheme depicted on the left is used in Tables II and III).

The AM-1 derived minimum energy structure was used as input for an *ab initio* calculation (GAUSSIAN 86)[9] at the 3-21 G level. The obtained geometry-optimized output structure differed from the AM1-derived structure only in terms of bond lengths (± 0.03 Å) and angles (± 0.4°), not in terms of torsional orientation. An *ab initio* transition state search, analogous to that indicated above on the AM-1 level, was carried out (GAUSSIAN 90) and the resulting output structure was very similar to the AM-1 calculated saddle-point structure (the indicated methyl group in the Figure was 28.4° out of the plane instead of 30.0°). The identity of this maximum as a true saddle-point was confirmed by the existence of one, and only one, negative eigenvalue of the force constant matrix. A comparison of the energies of the minimum energy and saddle point *ab initio* structures yielded a torsional barrier of 0.2 kcal/mole.

A single point calculation was carried out on the 6-31G level (GAUSSIAN 86) to optimize the electron distribution. Application of an electrostatic fitting routine (CHELPG)[10-11] afforded atomic charges. This fit was carried out with grid spacings of 1Å (338 points) and 0.5 Å (2786 points). Both runs yield similar values for the dipole moment of the molecule (4.5889 D vs. 4.5930 D) and for accessible atoms (aromatic H) but give different accounts for the aromatic carbon atoms, probably due to the poor resolution of the molecular surface as seen through the the more widely spaced grid. Thus the run with better grid resolution (0.5 Å) was chosen for the parametrization of atomic charges in the AMBER force field. To accomodate the united-atom model of the AMBER force field, charges on the carbon and hydrogen atoms of each methyl group were combined to give a united atom charge.

On inspection of the charge distribution in the molecule it is apparent that >97% of the positive charge of the ion is located on nitrogen and its surrounding atoms. Very little delocalization in the aromatic ring is visible, although an inductive polarization is observed (large negative charge on the 2- and 6- carbons of the aromatic ring in response to large positive charge on the 1-carbon). Thus, no changes were made in the intrinsic phenyl charges and C-H dipole moments of AMBER. Two new parameters were introduced to describe the bonds between nitrogen and aromatic carbon, and between nitrogen and united atom methyl as shown in Table I. Dipole moments were used to attenuate the input positive charge on nitrogen to give the proper charge distribution on the nitrogen and four neighboring carbons (united methyl). Force constants were taken from the normal AMBER file C(sp^3)-N(sp^3) bond and used for all four carbon nitrogren bonds.

With the modified parameters, the rotational barrier around the N - C(sp^2) single bond was negligible (0.1 kcal/mol). As the *ab initio* result for this rotational barrier is also extremely low, no corrective terms were introduced for this torsional rotation ($V_1 = V_2 = V_3 = 0$). Furthermore, no new terms were introduced for either

Table I: AMBER Parameters for the trimethylanilinium cation

Bond	bond length (Å)	force const. (kcal/mol $Å^2$)	bond dipole mom. μ (D)
$C(sp^2)$ - $N(sp^3)$	1.480	367.0	2.679
$C(sp^3)$ - $N(sp^3)$ [- $C(sp^2)$]	1.524	367.0	1.873

Table II: Computed and x-ray crystallographic interatomic distances (Å) and angles (°) for the trimethylanilinium cation (numbering scheme depicted in Figure 1)

Bond	Modified AMBER	3-21G	x-ray data[4a]		angle	Modified AMBER	3-21G	x-ray data[4a]
N - 2	1.507	1.508	1.504		8 - N - 9	106.1	107.2	108.0
N - 8	1.528	1.519	1.505		8 - N - 2	115.6	113.8	111.4
N - 9	1.527	1.526	1.509		9 - N - 10	108.6	109.5	109.2
N - 10	1.527	1.526	1.509		9 - N - 2	110.0	109.5	110.1
2 - 3	1.416	1.384	1.388		10 - N - 2	110.0	109.5	110.1
2 - 4	1.418	1.384	1.367		N - 2 - 4	122.5	120.0	121.5
3 - 5	1.405	1.382	1.379		N - 2 - 3	119.2	120.0	118.2
4 - 6	1.405	1.382	1.391		8 - N - 2 - 4	0.0	0.0	3.8
5 - 7	1.403	1.386	1.385					
6 - 7	1.403	1.386	1.373					

Table III: CHELPG and AMBER force field calculated atom and united methyl charges for the trimethylanilinium cation (numbering scheme depicted in Figure 1)

atom or united methyl	-charge- CHELPG[13]	-charge- modified AMBER		atom or united methyl	-charge- CHELPG[13]	-charge- modified AMBER
N	-0.172	-0.145		6C	-0.113	-0.150
8 (C + 3 H)	0.258	0.256		7C	-0.117	-0.150
9 (C + 3 H)	0.261	0.256		11H	0.165	0.150
10 (C + 3 H)	0.256	0.256		12H	0.218	0.150
2C	0.370	0.377		13H	0.155	0.150
3C	-0.355	-0.150		14H	0.172	0.150
4C	-0.222	-0.150		15H	0.164	0.150
5C	-0.039	-0.150				

bending or van der Waals interactions - those currently in the AMBER force field were used as necessary.[12] Table II presents a comparison of ab initio, x-ray crystallographic (counterion is di-m-bromo-dibromodicuprate (I)),[4a] and modified AMBER force field interatomic distances and angles for the trimethylanilinium cation. Table III lists a comparison of the electrostatic fitting routine (CHELPG) derived charges with those from the AMBER force field minimized structure.

In conclusion, we have completed *ab initio* and electrostatic fitting calculations on the trimethylanilinium cation and derived AMBER force field parameters based on our findings. These should be useful for molecular modeling of synthetic hydrophobic cavities which incorporate the anilinium cation subunit as well as other molecules which contain this chemical moiety.

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References and Notes:

1 a) Breslow, R.; Canary, J. W.; Varney, M.; Waddell, S. T.; Yang, D. *J. Am. Chem. Soc.* **1990**, *112*, 5212 and references therein. b) Koga, K.; Odashima, K. J. *Inclus. Phenom. Mol. Recogn. Chem.* **1989**, *7*, 53 and references threrein.

2 Some computer simulations of these type of hydrophobic cavities have been reported, although few details were given: Schneider, H.-J.; Kramer, R.; Theis, I.; Zhou, M.-Q. *J. Chem. Soc., Chem. Commun.*, **1990**, 276.

3 a) Thiem, H.-J.; Brandl, M.; Breslow, R. *J. Am. Chem. Soc.* **1988**, *110*, 8612. b) Thiem, H.-J., Ph.D. Thesis, Columbia University, 1991.

4 a) Andersson, S.; Jagner, S. *Acta Chem. Scand., Ser. A* **1985**, *39*, 799. b) Andersson, S.; Jagner, S. *Acta. Chem. Scand., Ser A* **1985**, *39*,423.

5 Weiner, P.; Kollman, P. *J. Comp. Chem.* **1987**, *2*, 287.

6 Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C.; *J. Comp. Chem.* **1990**, *11*, 440.

7 Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A.; GAUSSIAN 90, Revision H, Gaussian, Inc., Pittsburgh, PA, 1990.

8 a) Quantum Chemistry Program Exchange, Program No. 506, Indiana University, Bloomington, IN.. b) Altona, C. L.; Faber, D. H. *Top. Curr. Chem.* **1974**, *45*, 1.

9 Frisch, M.; Binkley, S.; Schlegel, B.; Raghavachari, K.; Martin, R.; Stewart, J. J. P.; Bobrowicz, F.; Defrees, D.; Seeger, R.; Whiteside, R.; Fox, D.; Fluder, E.; Pople, J. A.; GAUSSIAN 86, Release C; Carnegie Mellon University.

10 Brenemann, C. M.; Wiberg, K. B. *J. Comp. Chem.* **1989**, *11*, 361.

11 An adaption by C. Still and coworkers of the CHELPG program described in reference 10 was used.

12 Authentic AMBER parameters used (see Figure 1 for numbering scheme): N-2-4 and N-2-3 angles - KBnd1 = 70, ideal angle = 120; 2-N-8, 2-N-9, 2-N-10, 8-N-9, 8-N-10, and 9-N-10 angles - KBND1 = 50, ideal angle = 109.5, remaining angles and torsions: general benzenoid substructure.

13 The root mean square deviation for CHELPG charges is 0.017.