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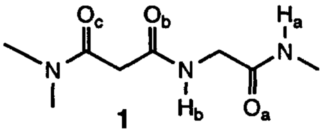
An AMBER* Study of Gellman's Amides

D. Quentin McDonald and W. Clark Still*
Department of Chemistry, Columbia University, New York, NY 10027.

Abstract: A new version of the AMBER molecular mechanics force field which was modified to reproduce *ab initio* data on small **peptides** is tested against recent experimental data on the conformational properties of simple di- and triamides (l-7) in methylene chloride.

In contrast to the situation with monofunctional organic molecules, there is little experimental data on the conformational energies of simple molecules having multiple polar functional groups. Studies like those of Gellman and coworkers1 on the conformations of di- and triamides l-7 are thus particularly valuable as a test of molecular mechanics force fields which are intended for use with biopolymers. Several of these molecules have been recently studied by semi-empirical* and molecular mechanics3 calculations. These calculations found that the lowest energy conformers of molecules such as 1 generally had maximal hydrogen bonding involving **7-membered** ring hydrogen bonds **(γ-turns).** These preferences persisted when methylene chloride solvent models were used. Interestingly, Gellman's experimental **IR** and NMR studies found little evidence of such y-turns in methylene chloride. Instead, he found other conformations, e.g. reverse turn-like hydrogen bonds in the form of g-membered rings, to be more heavily populated.

From a different quarter, *ab initio* calculations[4] on simple **peptides** independently suggested that y-turns are higher in energy than most molecular mechanics force fields predict. Consequently, we reparameterized the widely used AMBER force fields to reproduce the HF **6/31+G*** data on **glycine** and **alanine** amide reported by Pople, *et* a/.[4b] We designated the resulting force field as **AMBER***[6] and we show here how it performs on Gellman's amides.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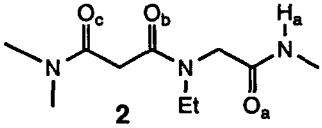
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For conformational analyses, we carried out two types of calculations using the new AMBER* force fields and **GB/SA** continuum model7 for chloroform. The first was a series of Monte Carlo conformational searchesa similar to those of Smith and **Vijayakumer**[3] which *were* intended to find all low energy conformations. The second was a series of molecular dynamics simulations in which hydrogen bonding was simply monitored and tabulated. The former calculation gives results which are primarily enthalpic while the latter gives actual populations based on free energies and is more relevant to Gellman's experiments. All calculations were carried out with our **MacroModel** and **BatchMin** molecular modeling programs.

Force Field Parameters. While AMBER and AMBER' have complete parameter sets for glycine-derived peptides, Gellman's compounds include other functionality for which no specific parameters have been reported. So that such systems could be modeled accurately, we carried out Gaussian 90 calculations on conformational minima and maxima of malonamide and propionamide.

Keeping the standard united-atom AMBER stretch, bend and nonbonded parameters for amides, we optimized parameters for the new O=C-C-C torsional arrays to reproduce the *ab initio* energies. The new torsional parameters along with *ab initio* and molecular mechanics energies are given below in **kcal/mol** (parentheses indicate maxima):

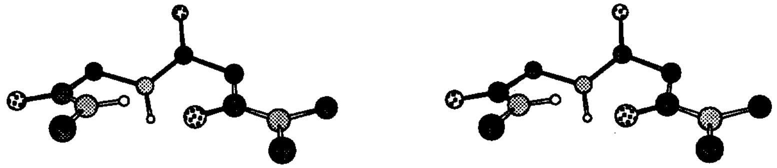
Propionamide:	HF/6-31G*	AMBER'
o=c-c-c: **0°**	0.0	0.0
o=c-c-c: 1170	1.4	**1.4**
O=C-C-C: **180°**	**(1.7)**	**(1.7)**

V1/2 = 0.0, **V2/2** = 1.44, **V3/2** = -0.41

Malonamide:	HF/6-31+G*	AMBER'
o=c-c-c: 47 **&** 1430	0.0	0.0
o=c-c-c: -122 **& 150°**	5.0	**4.7**
O=C-C-C: 0 & 0°	(12.1)	**(12.0)**

V1/2 = 2.15, **V2/2** = 0.40, **V3/2** = 0.0

Trlamides 1 and 2. According to experiment,[1a,b] the lowest enthalpy form of **1** in CH_2Cl_2 and the X-ray crystal structure have a g-membered hydrogen bond ($H_a \cdots O_c$ above), but conformations having **6-** and **7-membered** ring hydrogen bonds ($H_a \cdots O_b$, $H_b \cdots O_c$) are present in significant amounts with the **6-membered** form being predominant at room temperature. To find the conformational minima of **1,** we carried a **4000-step** Monte Carlo conformational search using AMBER* and **GB/SA** chloroform. We found five distinct conformations within the lowest 3 **kcal/mol** and the global minimum is shown below in stereo:



Thus the most stable conformation found is essentially the same as Gellman's X-ray structure of **1** and has a single hydrogen bond forming a g-membered ring. Slightly higher in energy at **+0.6** and **+0.9 kcal/mol** are two structures respectively having **6-** and **7-membered** ring hydrogen bonds. Extended forms having no hydrogen bonds lie **+2.0** and **+3.0 kcal/mol** above the global minimum.

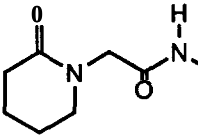
To obtain a better estimate of the populations of hydrogen bonded states of **1, we** subjected it to 10 ns molecular dynamics simulations at 200 K and 300 K with monitoring of each possible hydrogen bond.9 A hydrogen bond was counted present if it had an $H \cdots O$ distance **<2.5Å,** an N-H-O angle **>120°** and an **H···O=C** angle **>90°.** The results of the simulations are summarized below. AMBER* reproduces experiment better than the original AMBER and gives the **6-ring** form as predominant with increased amounts of the **9-ring** form at the lower temperature. On the other hand, the reported temperature dependence of the **6-ring** form was not reproduced by either force field.

Percentage of Population of 1 Having Given Hydrogen Bonds

	riginal AMBER		AMBER*	
	200K	300K	200K	300K
$H_a \cdots O_c$ (g-ring)	3%	5%	24%	12%
$H_a \cdots O_b$ (T-ring)	00%	67%	6%	6%
$H_b \cdots O_c$ **(6-ring)**	10%	15%	53%	45%

Experimental studies of 2 suggest it to exist primarily in a single conformation which is closely related to the global minimum of 1 with a g-membered ring hydrogen **bond.**[1a] Conformational searching as above finds eleven conformations of 2 within the lowest 3 **kcal/mol.** The global minimum and the next higher energy minimum **(+0.9 kcal/mol)** both have **9-ring** hydrogen bonds. The other nine conformations have **7-ring (γ-turn)** hydrogen bonds and start **+1.6 kcal/mol** above the global minimum. We could not use dynamics to study 2 because of the high barrier between the two tertiary amide conformers.

Thus calculations using AMBER* and **GB/SA $CHCl_3$** replicate the experimental hydrogen bonding patterns of 1 and 2 rather well. Even the temperature dependence of the O-ring hydrogen bond in 1 is reproduced by the simulation.



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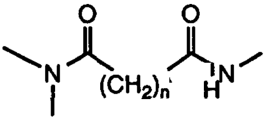

4 n = 1
5 n = 2
6 n = 3
7 n = 4

Glycyl **Lactam** 3. Infrared studies in **CH_2Cl_2** suggest two states for 3: one with a hydrogen bond (a y-turn) and one without. Both states appear to be significantly populated at 300 K. Furthermore, the NMR of 3 shows little temperature dependence and Gellman suggests that the two states are of comparable enthalpy.[1a,10] Conformational searching using AMBER' and **GB/SA $CHCl_3$** appears to be at variance with experiment because the global minimum, a hydrogen bonded form, is 2.7 **kcal/mol** lower in energy than the most stable non-hydrogen bonded energy minimum. Molecular dynamics, however, suggests that the global minimum is pan of a rather broad energy well including many states lacking well-defined hydrogen bonds, because a 10 ns dynamics simulation at 300 K finds that only 56% of the conformations of 3 are actually hydrogen bonded by the criteria defined above for 1. With the original AMBER, 81% of the population was hydrogen bonded. Thus despite the large energy difference between hydrogen bonded and non-hydrogen bonded *minimum* energy conformers, the hydrogen bonding populations calculated with the same force field at room temperature reflect what is observed experimentally.

Diamides 4-7. Studies of 4-7 in **CH_2Cl_2** indicate that the extent of intramolecular hydrogen bonding depends upon the spacing between the amide groups.[1d] Conformational searching using AMBER' and **GB/SA $CHCl_3$** finds multiple conformations for 4-7 but the lowest energy ones generally reflect what is observed experimentally. Thus diamides 4 and 7 which are more heavily hydrogen bonded show only hydrogen bonded conformations in the lowest 1 **kcal/mol:**

Diamide	**Experimental Structure**[1d]	**Conformers in Lowest 1 kcal/mol**	
		Having H-Bond	Having No H-Bond
4	H-Bonded (predominantly)	1	0
5	Extended (major) and H-Bonded	1	1
6	Extended (major) and H-Bonded	4	4
7	H-Bonded (50% **@ 200K)** and Extended	1	0

Because the -3 kcal/mol torsional barriers of 5-7 slow conformational interconversions too much for meaningful dynamics simulations, we could not compute the hydrogen bonded populations of these molecules. Diamide 4, however, is more mobile and dynamics finds that 77% of its conformations are hydrogen bonded at 300 K.Q

Conclusion. Though previous calculations on Gellman's amides used potential energy surfaces which unduly favored 7-ring hydrogen bonds (y-turns), the reported discrepancies between experiment and calculation in part reflect the inherent differences between room temperature experiments and calculations at absolute zero.[1e,2,3,10] For highly flexible molecules, conformational searching and energy minimizations are of limited utility for predicting room temperature properties of molecules, because populated states can be significantly different from the minimum energy conformers. For small molecules with only a few low barrier torsions, dynamics or Monte Carlo simulations provide a more realistic alternative: such simulations can be used to explore all conformational space and produce the correct populations of structures at a given temperature. With some of Gellman's amides, we were able to use this technique to estimate the populations of the variously hydrogen bonded forms by simply counting states. The precise result of such counting of course depends on how a hydrogen bond is defined, and a better approach would be to calculate the N-H vibrational frequency for each state. Such issues not withstanding, when all relevant functionality is parameterized to reproduce high quality *ab initio* data on small molecules and appropriate calculations are carried out, a picture of Gellman's amides emerges which is in semiquantitative agreement with experiment.11

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