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Communications

Amide-Amide Interactions in Solution 1. Monte Carlo Simulations

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An important problem in molecular peptide chemistry arises in attempts to provide a reliable description of amide-amide interactions such as the planar and vertical orientations of H-bonded amide pairs.[1] These two types of interactions are also deeply involved in the stability and conformational variability of DNA. However, the physical nature and origin of the interactions are somewhat unclear. Due to the rather different characteristics of amide interactions, no reliable theoretical study comparing the planar and vertical orientations of amide pairs has yet been performed.

Jorgensen[2] has investigated the self-affinity of N-methyl-acetamide (NMA) molecules in water and in chloroform at 25 ℃ and 1 atm. In chloroform, a single free energy well was observed with a depth of-3.5 kcal/mol at $r(N\cdots O)=2.8$ Å. The configuration of the two amides exhibited hydrogen bonding. However, in water NMA exhibited no net hydrogen bonding attraction and at short separations stacked geometries exhibiting a favorable dipole alignment are common. With primary amides, this kind of analysis has not yet done, because molecular interactions are complicated by the presence of a second hydrogen atom at nitrogen. Both *cis* and *trans* amide positions can influence intermolecular association, and in fact good interactions between the $-NH_2$ group and -C=O of acetamides would be possible only if the two amides are well oriented. In this short communication we present possible evidence that there are two types of geometries attainable in non-aqueous solutions by calculating "potentials of mean force" (pmf) for the association of acetamide by Monte Carlo simulations.

Monte Carlo simulations were performed with the BOSS program.[3] Three simulations were carried out for systems of two acetamide solute molecules placed in cubic boxes containing 247 water, 127 chloroform, or 126 carbon tetrachloride solvent molecules, respectively. OPLS potential functions were used for acetamide, chloroform, carbon tetrachloride and TIP4P water. In all calculations, the isothermal isobaric (NPT) ensemble was employed at 25 ℃ and 1 atm along with periodic boundary conditions. A cutoff distance of 8.5 Å was used for the aqueous solution, whereas 12 Å was adopted for the organic solvents. Free energy changes were computed by using statistical perturbation theory[4] as the two interacting solutes were separated by increments of 0.2 Å with the N···O distance as the reaction coordinate. The remaining computational details were identical to those for previously reported pmf determinations.[5,6] All atoms were explicitly considered except for hydrogens on carbon, and the Coulomb and Lennard-Jones interactions were included between the interaction sites. Internal bond lengths and angles were not varied, while the torsional motion about the central C-N bond of acetamide was sampled.[7] Otherwise, the motion of the solutes was unconstrained so that all intermolecular arrangements were accessible at the set values of the reaction coordinate. Each simulation covered at least 6×10^5 configurations of equilibration, followed by an additional 2×10^6 configurations of averaging. All computations were executed on a Silicon Graphics Iris Indigo workstation in our laboratory. The results were then analyzed with the Sybyl molecular modeling package.[8]

Figure 1 shows the pmf for acetamide dimer in water, chloroform, and carbon tetrachloride. In chloroform, two free energy wells are observed with depths of −4.2 kcal/mol and −1.9 kcal/mol at separation distances of 2.8 Å and 7.0 Å, respectively. Graphical views of several configurations occuring during the simulations show that at short separations the acetamides prefer to be oriented rather vertically to each other (Figure 2, top) and that at longer separations the amides associate in a planar dimeric conformation (Figure 2, bottom). In carbon tetrachloride, two free energy wells are also observed, but with deeper depths than in chloro-

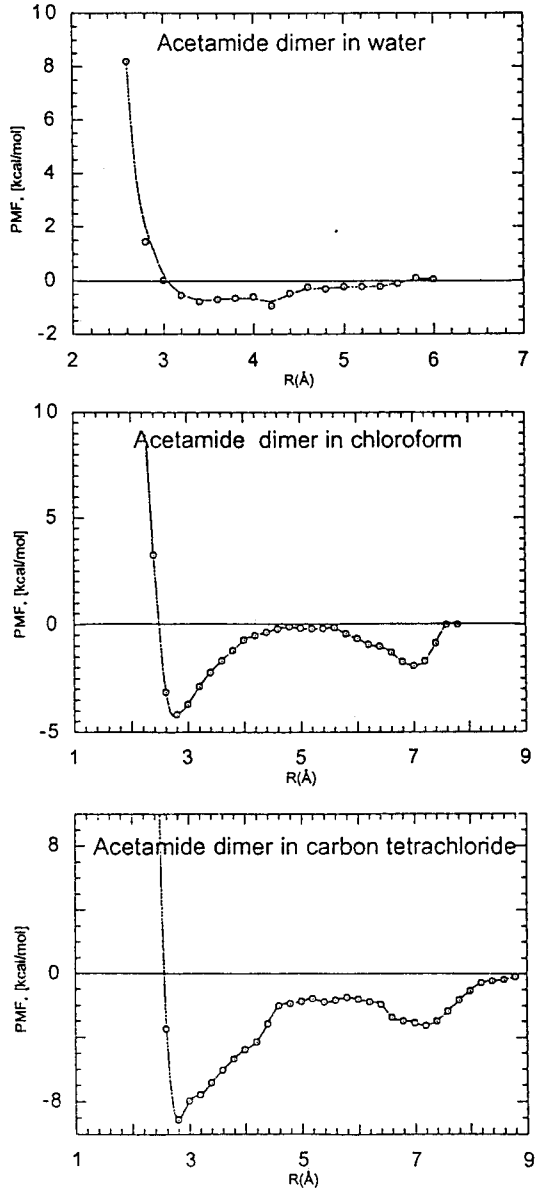

Figure 1. Calculated PMF for acetamide dimer in various solvents. R is N···O distance in Å.

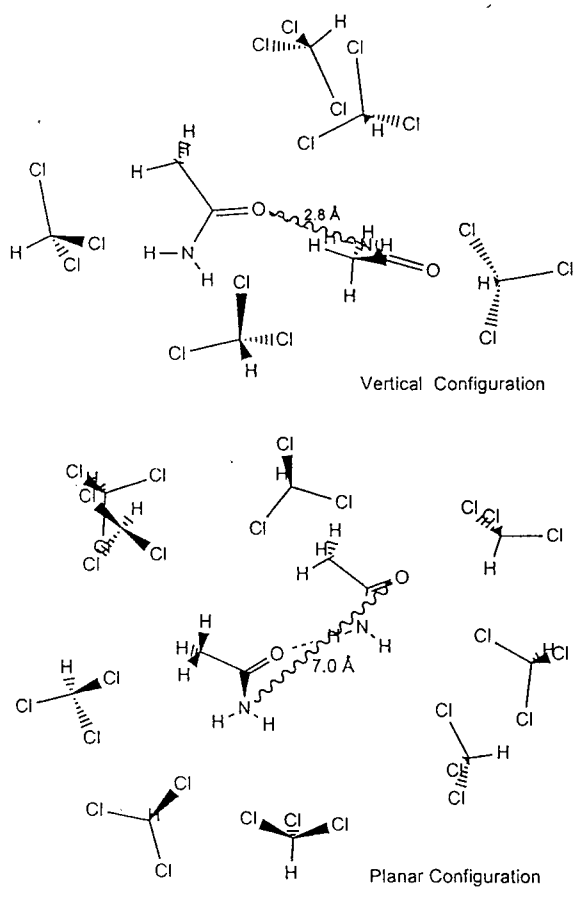

Figure 2. Configurations from the simulations of two acetamide molecules in chloroform with r(N···O) constrained to be 2.8 Å (top) and with r(N···O) (bottom) constrained to be 7.0 Å. Only a few of the solvent molecules in vicinities of solutes are shown.

form. The differences between chloroform and carbon tetrachloride reveal a solute-solvent interaction effect. Based on the potential function and parameter set used in these simulations, it is clear that interaction between the carbonyl oxygens of the acetamide and the hydrogens of chloroform might be possible. The inability of carbon tetrachloride to participate in this interaction is probably the primary factor which results in deeper free energy wells in carbon tetrachloride *vs.* chloroform.

As indicated in the Figures, the vertical arrangement between the two amide molecules is energetically more stable than the planar configuration. The net stabilization of the vertical structure corresponds to more than double that of the planar pair as indicated by the pmf. However, in water the amides exhibit only a slight net attraction.

In conclusion, the results presented here show the possibilities of the MC simulation technique to study both molecular associations[9] and the conformatioal flexibility of peptide and DNA molecules in solution. Further analysis of this type will enable the elucidation of detailed thermodynamics and structural features of solvated peptides and its environmental structure relationships. Further studies concerning the conformational properties of amides are currently in progress.

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Nonlinear Structure-Reactivity Correlations in the Aminolysis of *p*-Nitrophenyl Phenylacetates

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Structure-Reactivity relationships in the aminolysis[1~4] of aryl acetates have been important subjects of numerous kinetic studies since 1967. In the most of these studies, tetrahedral intermediate ($T^{\pm}$) by Hammett and Brønsted plots has been postulated in the reaction path. For instance, Jencks[4] reported the reaction of various amines with substituted-phenylacetates shows a change in the rate-determining step from break down to formation of $T^{\pm}$.

Castro[5] studied pyridinolyses of 2,4-dinitrophenyl acetate and methylphenyl-carbonate. The Brønsted plot obtained for the acetate system was curved but linear for carbonate system involving a $T^{\pm}$. The rate determining step of aminolysis[6] of arylthiol acetate, except the one for the reaction of *p*-nitrophenylthiol acetate with pipeidine, is decomposition of $T^{\pm}$ to product.

Recently, Castro[7] also studied aminolysis of O-ethyl-S(4-nitrophenyl) thiocarbonate, and found that Brønsted plot is nonlinear, *i.e.* $\beta_1=0.2$ and $\beta_2=0.8$ at high and low pK_a values, respectively, indicating the presence of $T^{\pm}$ and a change in the rate-determinig step.

We[8] studied, one of these subjects, the pyridinolysis of substituted phenyl acetates in acetonitrile and interpreted the mechanism in terms of a dissociative S_N2 mechanism involving a metastable tetrahedral intermediate. However, there are only a few works with the simple acetate compounds. In order to investigate further, in this paper we study the reaction of the *p*-nitrophenyl phenylacetate with secondary alicyclic amines by means of the Brønsted plot. We compare it with that studied in the pyridinolysis of aryl acetates, in the aim of evaluating the transition state and rate determining step for the α-substituted phenyl phenylacetate.

Reagents for the preparation, which were obtained from commercial sources, were used without purification. Piperidine, piperazine, morpholine and 1-formylpiperazine as nucleophiles were used reagent grade of Aldrich and purified according to standard procedures.[6] *p*-Nitrophenyl phenylacetate (mp 60-61.5 ℃, lit[9]. 60.5-61.6 ℃) was prepared from the reaction of phenylacetyl chloride with *p*-nitrophenol. Phenylacetyl chloride was obtained from the reaction of phenyl acetic acid (13.6 g, 0.1 mole) with thionyl chloride (8.5 mL, 0.118 mol) at 0 ℃ for 30 minutes. The pH was maintained either with sodium borate from Mallinchrodt and hydrochloric acid from Junsei. Water was purified by distilling deionized water twice after oxidation by $KMnO_4$, and acetonitrile was purified according to references.[8]

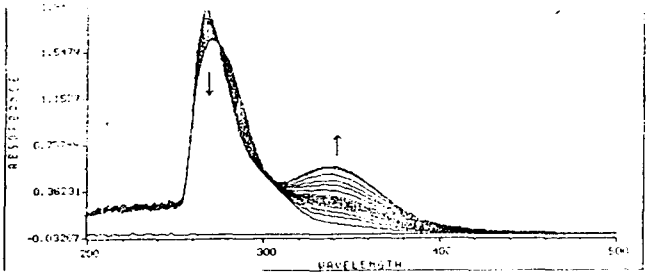

Figure 1. UV spectral change during the reaction of *p*-nitrophenyl phenylacetate(s) with 1-formyl piperazine(N) at pH=6.94. [S] $=2\times10^{-4}$ M, [N]=0.1 M.

Table 1. Experimental conditions and rate constants for the aminolysis of *p*-nitrophenyl phenylacetate in water at 40 ℃

amine	$10^2[N]_{tot}\cdot M$	pH	$10^3\ k_{obsd}\ (s^{-1})$
piperidine	0.300-1.30	8.40	2.21 - 3.69
	0.300-1.30	9.00	3.39 -97.5
piperazine	0.300-0.900	8.09	1.32 - 3.32
	0.300-1.30	8.45	2.42 - 5.18
morpholine	0.660-2.60	7.41	0.452- 1.47
	0.660-2.60	8.59	1.61 - 2.95
1-formylpiperazine	0.660-2.60	7.51	0.326- 0.816
	0.660-2.60	7.00	0.222- 0.765

The reaction was carried out under pseudo-first-order conditions with amines over 100 folds excess at least over substrate and studied spectrophotometrically (8452A Diode Spectrophotometer, Hewlett Packed) by following the release of *p*-nitrophenol at 340 nm, 40 ℃ and ionic strength 0.2 M KCl in the reaction of 1-formylpiperazine. The rate constants were calculated with 89532 K kinetic software (Serial No. 3205 G00380 attached above the Spectrophotometer).

The UV spectra for the reaction of *p*-nitrophenyl phenyl acetate (2×10^{-4} M) with 1-formyl piperazine (0.1 M) are shown in Figure 1.

The experimental conditions and rate constants of the reactions are described in Table 1, in which the rate constants increase with incresing concentration of nucleophile. Therefore, the kinetic law obtained for the present reactions is given by Eq. 1, where k_N is the rate constant for the aminolysis reaction, $[N]_{tot}$ is the concentration of amine. The values of k_N obtained from slopes of linear plots of k_{obsd} against $[N]_{tot}$ (free amine plus it's conjugated acid) at constant pH are shown in Table 2.

$$k_{obs}=k_N[N]_{tot} \quad (1)$$

Brønsted plot, logarithmic plot of k_N *vs.* pK_a, obtained in this work is curved, with the center of curvature near 10