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Association of *p*-toluyldimethylglycine in water

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ABSTRACT: For an aqueous solution of *p*-toluyldimethylglycine [$Me_2NCH(p\text{-}CH_3\text{-}C_6H_4)COOH$], at low concentrations or high temperatures, where solute–solute interactions are minimal, inversion about the amino group and the rate of tautomerization are relatively fast on the NMR time-scale. As a result, the dimethyl groups appear as a singlet in the NMR spectra. At high concentrations of the solute or low temperature, where there is an increase in solute–solute interactions via, more than likely, hydrogen bonds involving the acidic and basic functionalities, the rates of inversion and tautomerization are relatively slow. As a result, the two methyl groups are non-equivalent on the NMR time-scale. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: tautomerization; amino acids; hydrogen bonds; NMR spectroscopy; inversion

INTRODUCTION

Many compounds, such as drugs, are ionized to some extent at physiological pH in order to achieve biological activity.[1] Knowledge of the factors that influence the ionization of such compounds is necessary in order to a gain mechanistic understanding of their activity.[2] The extent of the ionization of compounds in solution is influenced not only by the structure of the compounds, but also by significant solute–solvent and solute–solute interactions that exist. Kamlet, Taft and co-workers have examined, in extensive detail, the source and nature of these types of interactions.[3] For α-amino acids, their limited solubility[4] in most solvents precludes a thorough analysis of the sources and nature of important solute–solvent and solute–solute interactions that exist. As a result, the properties of a wide variety of α-amino acids and their derivatives in different media are poorly understood. *N,N*-Dialkylated α-amino acids, in addition to being very important compounds in biological chemistry,[5] are ideal compounds that can be used to gain an understanding of the nature of solute–solvent and solute–solute interactions of α-amino acids; these two types of compounds have very similar structures. In addition, compared with most α-amino acids, dialkylamino acids are very soluble in a wide range of solvents.[6] In this work, we examined the nature of the association between *p*-toluyldimethylglycine molecules in water and the effects that temperature and concentration changes have on the equilibria of the tautomeric species. *p*-Toluyldimethylglycine is one in a series of substituted phenyldimethylglycine molecules which are currently being used in our laboratory to understand better the effects that substituents have on the properties of amino acids.

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EXPERIMENTAL

p-Toluyldimethylglycine was synthesized as outlined in the literature.[7] ^{1}H NMR spectra were recorded on an IBM (Bruker) NR/300 FT-NMR spectrometer.

RESULTS AND DISCUSSION

In D_2O, the ^{1}H NMR spectra of *p*-toluyldimethylglycine vary with both the concentration of the solute and temperature. Figure 1(A) shows the partial spectra of *p*-toluyldimethylglycine at different concentrations and Fig. 1(B) shows the partial NMR spectra of the same compound at different temperatures. The singlet at 2.1 ppm is that of the toluyl methyl group. From Fig. 1(A), the dimethylamino protons are equivalent at low concentrations of *p*-toluyldimethylglycine, but they are not equivalent at higher concentrations. From Fig. 1(B), the dimethylamino protons are equivalent at high temperatures, but they are not equivalent at low temperatures. The α-carbon of the dimethyl amino acid is chiral, hence at low rates of inversion of the free amine the diasteriotopic[8] *N*-methyls are magnetically non-equivalent in the ^{1}H NMR spectra. In contrast, the protonated amine can only invert through a tautomerization equilibrium with the free amine. Hence there are two

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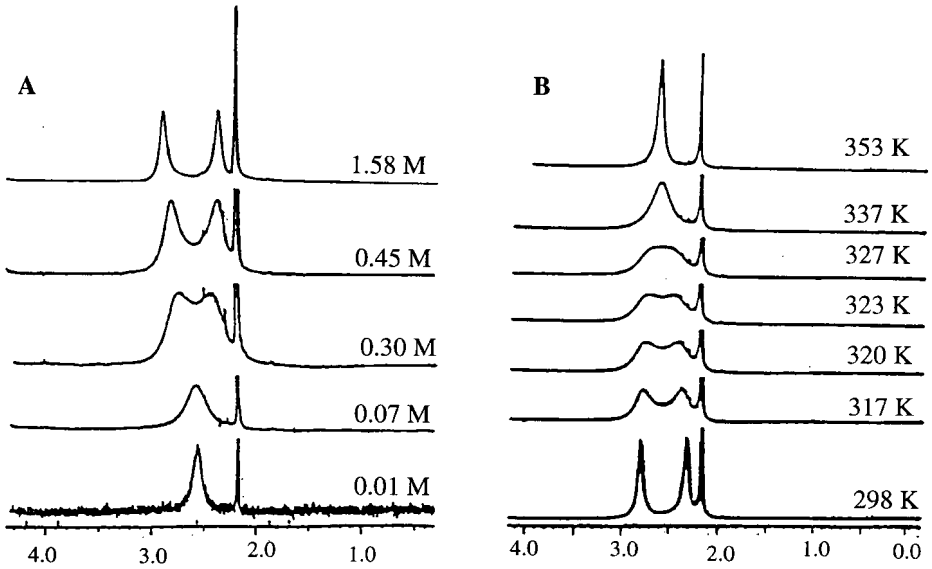

Figure 1. Partial 300 MHz spectra of *p* toluyldimethylglycine in D_2O. (A) Different concentrations at 298 K and (B) different temperatures of a 1.58 M solution

important equilibria (inversion and tautomerization) (Fig. 2), which must be considered to explain the spectra in Fig. 1.

In water, the tautomeric equilibrium for amino acids is known to favor the zwitterionic tautomer—the equilibrium constant is $10^{5.62}$ for glycine.[9] It has been shown experimentally and theoretically that water solvates the zwitterionic tautomer of amino acids very effectively.[10] Since water is considered to be one of the most polar protic solvents,[11] it will favorably solvate dipolar zwitterions. Hence it is reasonable to assume that the tautomeric equilibrium of *p*-toluyldimethylglycine in D_2O also favors the zwitterions and only a small concentration of free amine exists in the concentration and temperature range of this study. It is known that inversion about substituted amines is very fast;[12] thus, at low concentrations of *p*-toluyldimethylglycine where solute–solute interactions are expected to be minimal, and the lone pair of electrons on the nitrogen are not excessively hydrogen bonded, rapid inversion of the dimethylamino nitrogen of the neutral *p*-toluyldimethylglycine is expected. At low concentrations of the solute and at room temperature, fast tautomerization is expected. As a result of a rapid inversion rate combined with fast tautomerization (Fig. 2), the dimethylamino protons appear to be equivalent in the NMR spectra.

At higher concentrations of *p*-toluyldimethylglycine in water, the solute–solute association increases. The association is probably via specific and non-specific interactions,[13] but probably mainly specific interactions owing to the presence of an acidic hydrogen and a basic group. As a result of this close association between solutes, the lone pair of electrons on the nitrogen are involved in a hydrogen bond and the inversion rate about

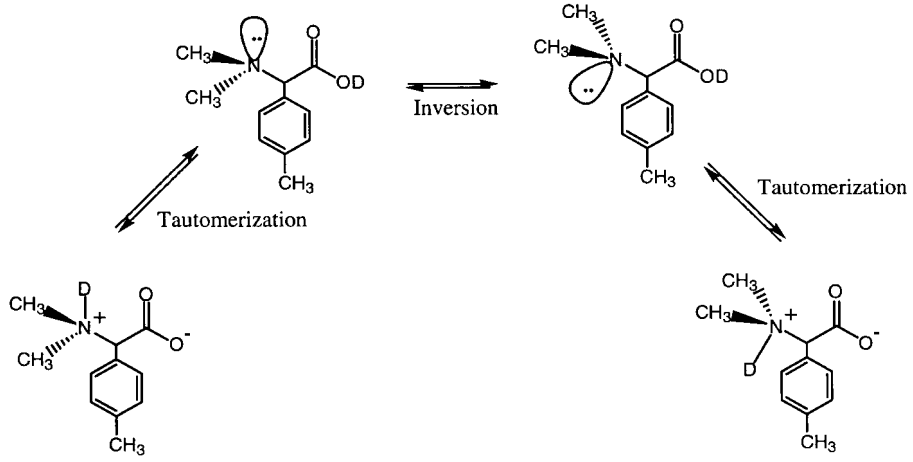

Figure 2. Equilibria of *p* toluyldimethylglycine in D_2O

the dimethylamino group is reduced, compared with that at lower concentrations. Another consequence of such a close solute–solute interaction is that the zwitterion is stabilized more than that in dilute solution, and thus a return to the neutral amino acid is more difficult owing to a higher activation barrier; hence the rate of tautomerization is reduced also at higher concentrations. It is difficult to determine which of the rates is affected more as a function of concentration, but a reduced rate of inversion and tautomerization renders the dimethyl protons non-equivalent on the NMR time-scale.

From the results shown in Fig. 1(B), there is indication that the association between the solute molecules is more than likely via hydrogen bonds. It is known that hydrogen bonds are sensitive to temperature[14] and from the temperature-dependent spectra in Fig. 1(B) the two signals for the *N*,*N*-dimethylamino hydrogens coalesce to a single signal at high temperatures. At low temperatures (which is also at a high concentration of the solute), owing to strong association through hydrogen bonds of the solute species, the amino acid exists as effective aggregates. Hence the appearance of two signals at low temperatures is caused by a slow rate of inversion and tautomerization. As the temperature is raised, however, the effectiveness of the hydrogen bonds is reduced and the rates of inversion of the amino groups, and also the tautomerization, are increased, and, as a result, the dimethyl groups appear equivalent in the NMR spectra.

In summary, at low concentrations of *p*-toluyldimethylglycine in water or high temperatures, solute–solute interactions are minimal, the rates of inversion about the amino groups and tautomerization are relatively fast on the NMR time-scale and the dimethyl groups appear as a singlet. At high concentrations of the solute or low temperature, it is expected that the solute–solute association should be strong, rendering very stable zwitterion aggregates, similar to that found in the crystal structure of dimethylamino acids (A. D. Headley, S. D. Starnes and B. R. Whittlesey, unpublished results).

As a result of this strong association, the rates of inversion and tautomerization are reduced and the two methyl groups are non-equivalent on the NMR time-scale. Even though the formation of the specific and non-specific interactions may be the major driving force for the association of these amino acids, their hydrophobic/hydrophilic nature may serve to orient the molecules such that there are interactions between the carboxylic acid and amino functionalities. Similar NMR temperature and concentration dependence spectra were not observed for α-alkyldimethylamino acids, such as *N*,*N*-dimethylvaline, which do not have as hydrophobic a side-chain.[15] There may be two explanations for this observation: (a) the diasteriotopic shift caused by the isopropyl group is not great enough to be detected; or (b) the hydrophobic effect of the isopropyl group is not great enough to cause aggregation of the molecules. Ongoing investigations are being carried out in our laboratory to delineate the contributions of these effects.

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