

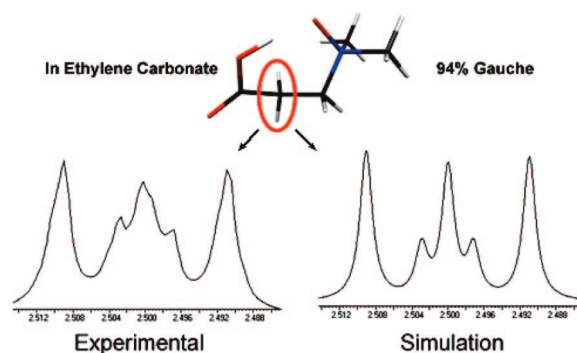
## Conformational Preferences of 3-(Dimethylazinoyl)propanoic Acid as a Function of pH and Solvent; Intermolecular versus Intramolecular Hydrogen Bonding

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The conformational equilibrium of 3-(dimethylazinoyl)propanoic acid (DMAPA, azinoyl =  $N^+(O^-)$ ) has a weak pH-dependence in  $D_2O$ , with a slight preference for trans in alkaline solutions. The acid ionization constants of the protonated amine oxide and carboxylic functional groups as determined by NMR spectroscopy were  $7.9 \times 10^{-4}$  and  $6.3 \times 10^{-6}$ , respectively. The corresponding value of  $K_1/K_2$  of  $1.3 \times 10^2$  is not deemed large enough to provide experimental NMR evidence for a significant degree of intramolecular hydrogen bonding in  $D_2O$ . Conformational preferences of DMAPA are mostly close to statistical (gauche/trans = 2/1) in other protic solvents, e.g., alcohols. However, the un-ionized form of DMAPA appears to be strongly intramolecularly hydrogen-bonded and gauche in aprotic solvents.

### Introduction

Study of conformational preferences of 1,2-disubstituted ethanes in solvents with different properties can provide information about the interplay of intra- and intermolecular forces between functional groups and solvent molecules.<sup>1</sup> To this end, the conformational preferences of 3-(dimethylazinoyl)propanoic acid (DMAPA), Figure 1, have been investigated as a function of both pH and solvent properties with the aid of NMR chemical shifts and spin–spin couplings. The present study is quite complementary and parallel to research on the diamine oxide,<sup>2</sup> *N,N,N',N'*-tetramethylethylenediamine-*N,N'*-dioxide, or 1,2-di(dimethylazinoyl)ethane, and it is of substantial interest to compare the behavior of the two compounds.

A simple and useful view of solvent–solute relationships is to think of solute molecules as occupying cavities in solvents

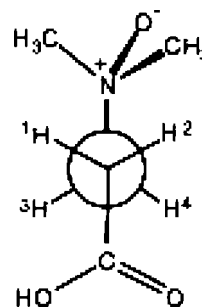
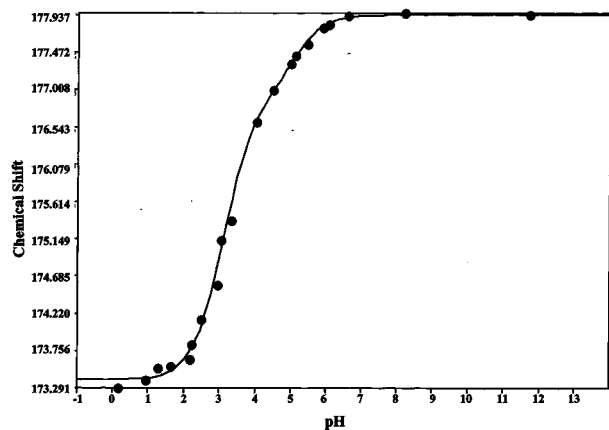
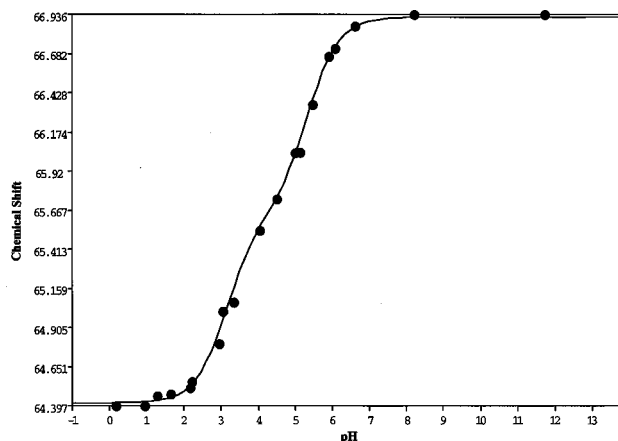


FIGURE 1. *trans*-3-(Dimethylazinoyl)propanoic acid (DMAPA).

surrounded by a continuum of solvent of constant dielectric constant. This way of dealing with electrostatic and polar effects of solutes was introduced by Kirkwood and Westheimer<sup>3a,b</sup> in their pioneering calculations of average end-to-end distances between carboxylate groups in water from changes in electrostatic interactions between the diacid, monoanion, and dianion

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a)  $^{13}\text{C}$  (COOH)b)  $^{13}\text{C}$  (N-CH<sub>2</sub>)

**FIGURE 2.**  $^{13}\text{C}$  chemical shifts of the (a) carboxyl carbon and (b) methylene carbon  $\alpha$  to the amine oxide groups of 3-(dimethylazino)lpropanoic acid over a pH range of 0.1–11.7.

forms of dicarboxylic acids.<sup>3</sup> Further calculations of electrostatic interactions between carboxylate and polar groups were made by Westheimer and Shookhoff.<sup>4</sup> One might also consider intermolecular interactions between solute and solvent molecules at the surfaces of the cavities. Such interactions were not explicitly taken into account by Kirkwood and Westheimer in their calculations for water solutions. They also neglected the possibility of intramolecular hydrogen bonding for the monoanions, an omission later challenged<sup>5</sup> but nonetheless shown to be valid for the systems involved.<sup>6</sup> When solvents other than water are used, especially aprotic solvents, which have been quite well studied for DMSO, many 1,4-dicarboxylic acids show very large differences in their  $K_1/K_2$  ratios that are only attributable to intramolecular hydrogen bonding of the monoanions.<sup>17</sup>

Determination of the conformational preferences of DMAPA requires analysis of a time-averaged mixture of trans and the two enantiomeric gauche conformations resulting from rapid rotation about the C2–C3 bond. As an amine oxide, DMAPA has formal positive and negative charges on nitrogen and oxygen atoms, respectively. It is not easy to look at its molecular structure and a priori divine how the highly polar amine oxide group and the two bulky, at best only slightly polar, methyl groups will collectively interact with the carboxyl and carboxylate to determine conformational preferences as a function of solvent and pH.

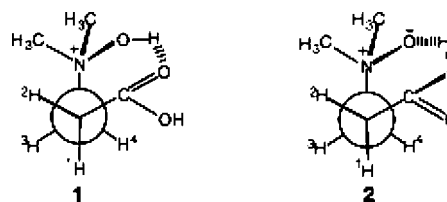
The conjugate acid and neutral, but not anionic, forms of DMAPA have the potential to exist as two intramolecularly hydrogen-bonded forms, **1** and **2**. To form **2**, the carboxylic acid group must change its hydroxyl configuration from the favorable *Z*-conformer to the less favorable *E*-configuration, which brings an energetic penalty of 3–5 kcal/mol, thus decreasing the expected hydrogen-bond stabilization of **2**.<sup>8–10</sup> The possible role of **1** will be discussed later.

The crux of approaches to conformational analysis of 1,2-disubstituted ethanes as a function of the characteristics of the substituents is to possess a reliable method for at least estimating the positions of conformational equilibria in solution. A useful semiempirical method for this purpose involves measurement of the vicinal coupling constants and then uses Altona's modification of the Karplus equation<sup>11</sup> to estimate the  $J_{ij}$  couplings between the X-CH<sub>2</sub>-CH<sub>2</sub>-Y protons for each conformer of the DMAPA species. The Altona approach allows one to assign dihedral angles ( $\theta_1$  and  $\theta_2$ ) and empirical

electronegativity variables ( $\lambda$ ), determined for substituents X and Y from the proton–proton couplings of CH<sub>3</sub>CH<sub>2</sub>X and CH<sub>3</sub>CH<sub>2</sub>Y in solvents of interest.<sup>11</sup>

An independent indication of intramolecular hydrogen bonding in aqueous solution can be deduced from perturbations of the ionization constants of the protons involved in forming the hydrogen bond. For this, Ebersson<sup>12</sup> and McCoy<sup>13</sup> suggest if  $K_1/K_2 > 10^4$  for dicarboxylic acids in water, one can expect significant intramolecular hydrogen bonding because stabilization of the monoanion by hydrogen bonding should increase  $K_1$ , and in the second ionization, the loss of the hydrogen bond should decrease  $K_2$ .

In this research, the conformational preferences of DMAPA were examined (1) as a function of ionization state<sup>14</sup> in D<sub>2</sub>O and (2) as a function of solvents, which have different hydrogen-bonding capabilities and polarities.



## Results and Discussion

### Conformational Analysis of DMAPA as a Function of pH. The $pK_a$ values of DMAPA were determined from the

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(14) Ongoing experiments performed in H<sub>2</sub>O have shown conformational preferences similar to those observed in D<sub>2</sub>O.

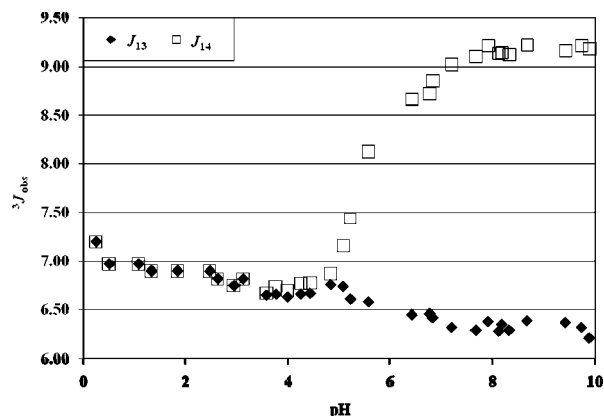


FIGURE 3. Coupling constants  $J_{13}$  and  $J_{14}$  of 3-(dimethylazino)propanoic acid as a function of pH.

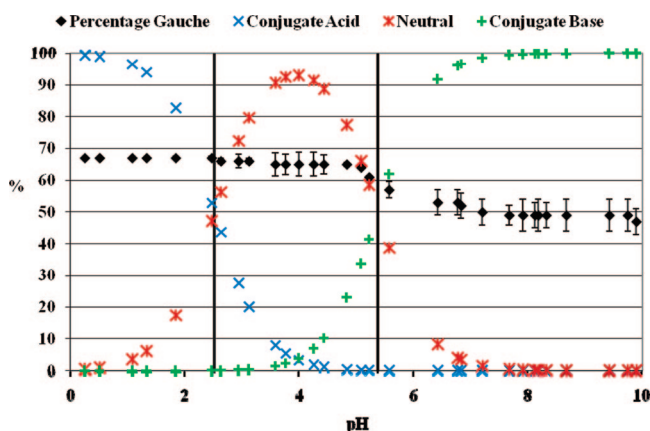


FIGURE 4. Percentages of gauche conformers with an assumed dihedral angle of  $60^\circ$  for 3-(dimethylazino)propanoic acid in  $D_2O$  as a function of pH (solid diamonds). Error bars correspond to the uncertainty of percent gauche calculated from observed coupling constants. Vertical lines across the graph correspond to  $pK_1$  and  $pK_2$  as calculated from data in Figure 2. Also displayed are the percentages of different protonation states of DMAPA as a function of pH.

changes of  $^{13}C$  chemical shifts of the carboxyl carbon and the methylene carbon  $\alpha$  to the amine oxide substituent as a function of pH (Figure 2) and were iteratively fitted to obtain average values for the carboxyl and amine oxide groups. The  $pK_1$  and  $pK_2$  values calculated from Figure 2a were  $3.12 \pm 0.09$  and  $5.11 \pm 0.09$ , respectively, with a correlation coefficient of 0.999. Figure 2b provided values of  $3.10 \pm 0.09$  and  $5.34 \pm 0.09$ , for  $pK_1$  and  $pK_2$ , respectively, with a correlation coefficient of 0.996. The average  $pK_a$  from the two groups were  $pK_1 = 3.11 \pm 0.09$  and  $pK_2 = 5.22 \pm 0.11$ . The value of  $pK_2$  is interesting when compared to the  $pK_1$  of 4,4-dimethylpentanoic acid, 4.83,<sup>15</sup> and 3-*N,N,N*-trimethylaminopropanoic acid, 3.27,<sup>16</sup> and will be discussed further.

The methylene proton vicinal coupling constants (Figure 3) showed changes with pH as well. An iterative fit of the calculated percentages of gauche plotted in Figure 4 leads to  $pK_1$  and  $pK_2$  constants of  $2.52 \pm 0.79$  and  $5.37 \pm 0.79$ , respectively, with a correlation coefficient of 0.986. However, the large standard deviation of 0.79 suggests that it is better to rely on the chemical-shift data.

TABLE 1. Measured Vicinal  $^1H$ – $^1H$  Coupling Constants for 3-(Dimethylazino)propanoic Acid as Conjugate Diacid, Monoacid, and Anion in a Selection of Deuterated Protic and Aprotic Solvents

| solvent            | conjugate acid, $^3J_{obs}$ , Hz |          | neutral, $^3J_{obs}$ , Hz |          | conjugate base, $^3J_{obs}$ , Hz |          |
|--------------------|----------------------------------|----------|---------------------------|----------|----------------------------------|----------|
|                    | $J_{13}$                         | $J_{14}$ | $J_{13}$                  | $J_{14}$ | $J_{13}$                         | $J_{14}$ |
| $D_2O$             | 6.9                              | 6.9      | 6.6                       | 6.7      | 6.7                              | 8.7      |
| MeOD               | 7.2                              | 7.2      | 6.1                       | 6.1      | 6.3                              | 8.8      |
| EtOD               | 7.1                              | 7.1      | 5.9                       | 5.9      | 6.2                              | 8.3      |
| <i>i</i> -PrOD     | 7.1                              | 7.1      | 5.2                       | 5.2      | 5.4                              | 6.3      |
| <i>t</i> -BuOD     | 7.0                              | 7.0      | 5.6                       | 5.6      | 6.4                              | 8.0      |
| ethylene carbonate | 6.7                              | 7.6      | 8.5                       | 2.6      | 7.2                              | 3.7      |
| DMSO               | 7.5                              | 7.5      | 8.5                       | 2.7      | 7.1                              | 4.1      |
| acetonitrile       | 7.1                              | 7.3      | 8.5                       | 2.5      | 7.2                              | 3.8      |

The vicinal proton–proton coupling constants of Figure 3 were used to calculate equilibrium percentages of gauche DMAPA with a dihedral angle of  $60^\circ$  using the Altona procedures for calculating  $\lambda$  constants and the vicinal coupling constants.<sup>17</sup> Further discussion of the  $\lambda$  constant determinations is given in the Experimental Section. The  $\lambda$  values for the carboxyl and amine oxide substituents, given in the Experimental Section, were applied to the calculated coupling constants and used to determine the percentages of gauche of DMAPA across a range in pH as shown in Figure 4.

The plot in Figure 4 shows a gauche range from 47% to 67% over a measured pH range of 0–12 for DMAPA. The gauche preferences for DMAPA can be separated into three distinct regions, corresponding to differently protonated DMAPA species. From pH 0 to 3, the statistical percentage gauche value is observed, indicative of protonated DMAPA but not **1**, which would be strongly gauche. There is an insignificant decrease from the statistical gauche value from pH 3 to 5, where the neutral species predominates, while the decrease in gauche population observed at pH greater than 5 corresponds to the conjugate base.

The  $pK_1$  and  $pK_2$  values for DMAPA translate to a moderate  $K_1/K_2$  of  $1.26 \times 10^2$ , definitely smaller than Ebersson and McCoy's  $K_1/K_2$  cutoff of  $10^4$ . This suggests that DMAPA will not appear in its NMR spectrum to be significantly intramolecularly hydrogen-bonded as in structure **2** in aqueous solutions, which is in accord with the conformational data and the fact that the monoanion of succinic acid does not exhibit intramolecular hydrogen bonding in water with a  $K_1/K_2 > 24$ .<sup>18</sup> Comparison between the  $pK_2$  of DMAPA and  $pK_a$  of 4,4-dimethylpentanoic acid is of interest because hydrogen bonding would be expected and does raise DMAPA's  $pK_2$  above that of the alkanolic acid. This behavior suggests that the  $10^4$  cutoff may not be applicable in systems with dissimilar functional groups.<sup>1</sup> The  $K_1/K_2$  for DMAPA is smaller than that of 1,2-di(dimethylazino)ethane,  $9.1 \times 10^3$ , the latter having a conformational preference as expected for intramolecular hydrogen bonding in its monoconjugate acid form.<sup>2</sup>

**Conformational Preference as a Function of Solvent.** The vicinal-proton coupling constants for the central  $CH_2$ – $CH_2$  resonances for DMAPA in several protic and aprotic solvents are listed in Table 1. As in previous work,<sup>19</sup> the assignment of  $J_{13}$  and  $J_{14}$  can be reversed without change in the simulated

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**TABLE 2.** Calculated Equilibrium Percentages of the *Gauche* Conformer of 3-(Dimethylazino)lpropanoic Diacid, Acid, and Anion in Solutions of Deuterated Protic and Aprotic Solvents

| solvent            | dielectric constant | conjugate acid, $\theta = 60^\circ/65.0^\circ$ <sup>a</sup> |         | neutral, $\theta = 60^\circ/88.8^\circ$ <sup>a</sup> |         | conjugate base, $\theta = 60^\circ/59.2^\circ$ <sup>a</sup> |         |
|--------------------|---------------------|---|---------|--|---------|---|---------|
|                    |                     | % <i>gauche</i>   | $\pm^b$ | % <i>gauche</i>                                      | $\pm^b$ | % <i>gauche</i>   | $\pm^b$ |
| D <sub>2</sub> O   | 78.5                | 67/62   | 0/1     | 65/56  | 4/8     | 56/56   | 8/7     |
| MeOD               | 32.6                | 67/63   | 0/3     | 67/49  | 0/11    | 50/51   | 0/0     |
| EtOD               | 24.3                | 67/63   | 0/3     | 67/47  | 0/14    | 52/53   | 2/2     |
| <i>i</i> -PrOD     | 18.3                | 67/64   | 0/5     | 67/43  | 0/21    | 52/53   | 19/19   |
| <i>t</i> -BuOD     | 12.1                | 67/66   | 0/8     | 67/46  | 0/15    | 57/58   | 4/4     |
| ethylene carbonate | 90.5                | 62/57   | 4/4     | 110°/88  | 0/0     | 87/89   | 9/9     |
| DMSO               | 47.2                | 72/68   | 14/13   | 110°/88  | 3/3     | 85/87   | 7/7     |
| acetonitrile       | 36.6                | 69/64   | 7/7     | 110°/88  | 1/1     | 87/89   | 8/8     |

<sup>a</sup> Dihedral angles derived from estimated conformational preferences assuming reasonable values of  $\theta$  for the conjugate acid, neutral, and conjugate base forms of DMAPA. <sup>b</sup> The  $\pm$  columns represent the percentage range of uncertainty for the calculated percentage of *gauche* for each solvent. <sup>c</sup> These values reflect an incorrect choice of dihedral angle. Some discussion below and also detailed elsewhere.<sup>1</sup>

spectrum. Two independent sets of *gauche*-to-*trans* ratios can be obtained from  $J_{13}$  and  $J_{14}$ ,<sup>20</sup> by comparing these  $J$  values with the corresponding Altona estimates of corresponding coupling constants for each conformer. The *gauche*-*trans* ratio with the lower-magnitude uncertainty for each pair is taken as the correct one.<sup>21</sup> The estimated preferences for the *gauche* conformer of DMAPA for the selected solvents are summarized in Table 2.

The closely statistical conformational preferences for the conjugate acid of DMAPA for protic solvents with assumed dihedral angles of 60° or 65° appear to give only a very slight edge to 60° angles (Table 2). The data suggests that steric hindrance does not cause *gauche* preferences less than the statistical values. In aqueous solutions, similar effects have been observed for the analogous 3-(*N,N,N*-trimethylammonium)propionic acid.<sup>22</sup> The more sterically challenging and less polar *tert*-butyl group of 4,4-dimethylpentanoic acid only leads to approximately 70:30 *trans*:*gauche* preferences in both protic and aprotic solvents.<sup>19</sup> Apparently, planar carboxylate groups can rotate and orient themselves so as to alleviate the steric demands expected for the *gauche* conformation. In contrast, compounds possessing two bulky tetrahedral groups, such as 2-(*N,N,N*-trimethylammonium)ethanesulfonic acid<sup>22</sup> and *N,N,N*-(3,3-dimethylbutyl)trimethylammonium cation,<sup>23</sup> show relatively strong preferences for *trans*. More significant differences in *gauche* preference are found between protic and aprotic solvents for the neutral DMAPA (Table 2). Thus, intramolecular hydrogen bonding between the carboxyl hydrogen and the amine oxide oxygen are expected to lead to a *gauche* preference. This will be true provided that the solvent is not strongly protic (particularly water) and thus does not weaken the *gauche* preferences for DMAPA by strong intermolecular hydrogen bonding to the solute in competition with intramolecular hydrogen-bond formation between the amine oxide and/or the carboxyl groups of DMAPA. Excellent examples of this effect are seen with monosuccinate.<sup>1,10,21</sup> Because the monosuccinate and neutral species of DMAPA are similar in regard to ring size for intramolecular hydrogen bonding and both have a carboxyl substituent proximate to a negatively charged oxygen, neutral DMAPA should be expected to have a similar increase

changing from protic to aprotic solvents. This is indeed observed, with 88% *gauche* in DMSO assuming  $\theta_g = 88.8^\circ$  and 110% for  $\theta_g = 60^\circ$  consistent with intramolecular hydrogen bonding between the amine oxide to carboxylic acid and *gauche* dihedral angles greater than 60°.

For the conjugate base, there is no possible O–H···O intramolecular hydrogen bonding and one would expect the *gauche* population to be less than the statistical 67% in both aprotic and protic solvents, as the result of electrostatic interactions between oxide and carboxylate groups. This is supported for protic solvents with changes in dihedral angle as indicated in Table 2, where *gauche* preferences for the conjugate base in protic solvents fall in the range of 50–58% for 60° and 59.2° dihedral angles. In aprotic solvents, however, the conjugate base of DMAPA shows a significant increase in *gauche* preferences in the range of 85–89%. The succinate dianion, which has electrostatic repulsion between its negative carboxylate substituents, is less than 60% *gauche* in aprotic and protic solvents if near 60° dihedral angles are chosen.<sup>18,24</sup> Although an analog of succinate dianion from a hydrogen-bonding perspective, the conjugate base of DMAPA has a larger preference for *gauche* in aprotic solvents, perhaps because of the difference between a pair of charged functional groups to a single negative carboxylate ion. Here, there is a possibility of electrostatic attraction between the carboxylate and the positive amine oxide nitrogen, if the conformation is geometrically as calculated (vide infra) and shown in Figure 5.

To further explore the geometric feasibility of intramolecular hydrogen bonding and charge-dipole interactions for DMAPA, gas-phase computations were made on the *gauche* conformers of the conjugate acid, neutral, and conjugate base of DMAPA at the B3LYP/6-31G+(d,p) level of theory using GAMESS.<sup>25</sup> The conjugate acid species as shown in Figure 6a (**1**) was calculated as being capable of a hydrogen-bonded geometry with backbone dihedral angles in the 65° range, an O–H···O angle of 166.5°, and an O–O distance of 2.61 Å, all of which suggest hydrogen bonding should occur in the gas phase, even if not observed in aprotic solvents (Table 2). The neutral DMAPA molecule was computed to have a similar hydrogen-bonded geometry in the gas phase. However, the dihedral and H–O···H angles widened to 88.8° and 172.3°, respectively. The O–O

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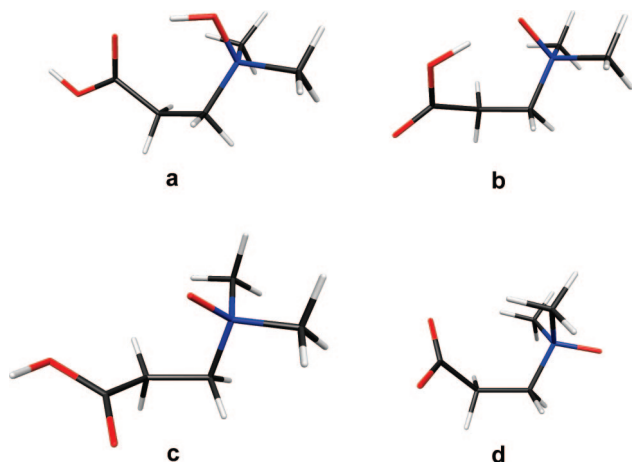
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**FIGURE 5.** Computed gas-phase structure of 3-(dimethylazinoyl)propanoic acid for the anionic gauche species. The distances between the nearest carboxylate oxygen and the amine oxide nitrogen and the methyl protons are 3.5 and 2.4 Å, respectively, for both methyl groups. The carboxylate carbon–nitrogen distance is 3.2 Å.



**FIGURE 6.** Computed gas-phase structures of 3-(dimethylazinoyl)propanoic acid for (a) the conjugate acid, **1**, (b) intramolecular hydrogen-bonded neutral, **2**, (c) neutral Z-carboxyl, and (d) anionic gauche species.

distance decreased to 2.54 Å, suggesting stronger hydrogen bonding than for the conjugate acid. A secondary minimum energy form (**6c**) was found as a neutral non-hydrogen-bonded gauche conformer with the carboxylic acid hydroxyl in the Z-conformation and the dihedral angle reduced to 77.4°. However, this geometry was computed to be less stable by 7 kcal/mol. The anion, lacking the potential for hydrogen bonding, is calculated to have a gauche geometry with a dihedral of 59.2° and the amine oxide rotated so that the N–O bond points away from the carboxylate. The carboxylate oxygen is twisted toward the nitrogen and is in van der Waals contact with the methyl hydrogens. Using the charges calculated for the nitrogen and oxygen atoms of the amine oxide and the nearer of the carboxylate oxygens,<sup>26</sup> a stabilization of 7.2 kcal/mol is calculated for the charge-dipole interaction in **6d**. These geometries are depicted in Figure 6. The gas phase can be viewed as the limiting case of a low-dielectric, non-interacting solvent. However, it must be understood that calculations in the gas phase at any level of theory do not answer the question of whether these interactions are energetically favorable in the common protic and aprotic solvents in which the conformations were studied.

(26) No attempt has been made to correct for the dielectric properties of the molecule or the medium, so this value should be viewed as an upper bound.

The data in Table 2 show that with the conjugate acid, there is little net effect on the conformational equilibria in protic and aprotic solvents, which implies that intramolecular hydrogen bonding is not a dominant force for this species, despite gas-phase calculation of **6a** as a significant species. For DMAPA itself, intermolecular hydrogen bonding to protic solvents outcompetes intramolecular hydrogen bonding, similar to what is observed with protonated DMAPA but quite differently from monosuccinate in the same alcoholic solvents used in these studies.<sup>1,21</sup> Meanwhile, the amine oxide oxygen proves to be a better hydrogen-bond acceptor than lone pairs of the aprotic solvents employed in these experiments and thus produces the observed preference toward the gauche form in aprotic solvents. The conjugate base can accept hydrogen bonds from alcohol solvents, which should shift conformational preferences toward statistical levels, while in aprotic media, it is our conjecture that a conformer such as is shown in Figure 5 could stabilize the gauche structure via charge-dipole interactions.<sup>27</sup>

## Conclusions

In summary, NMR spectroscopy indicates that the conjugate acid and neutral forms of 3-(dimethylazinoyl)propanoic acid have essentially statistical preferences for gauche in water and alcohols as protic solvents, unperturbed by intramolecular hydrogen bonding. In water, the conjugate acid predominates at pH 0–3.11 and the neutral species predominates at pH 3.11–5.22 with a statistical preference for gauche in both cases. The anionic form of DMAPA, which is favored at pH greater than 5.22, has an increased preference for trans, most likely as the result of intermolecular hydrogen bonding to protic solvents. In aprotic solvents, substantial gauche preferences are observed for both the neutral and anionic forms but not for the protonated DMAPA. With neutral DMAPA in aprotic solvents, intramolecular hydrogen bonding strongly stabilizes the gauche conformer, while for the anion, a smaller preference observed for the gauche conformer may involve attraction between the carboxylate and the amine oxide nitrogen.

## Experimental Section

**Synthesis of 3-(Dimethylazinoyl)propanoic acid.**<sup>28</sup> *N,N*-Dimethylhydroxylamine hydrochloride (2.4 g) was dissolved in methanol (25 mL), and triethylamine (5.1 mL) was added with stirring. Excess acrylic acid (3.5 mL) was dissolved in methanol (25 mL), and triethylamine (5.1 mL) added with stirring. The two methanolic solutions were mixed and stirred overnight at room temperature. The reaction mixture was concentrated in vacuo and heated with acetone (150 mL), allowed to cool, and filtered. The acetone treatment was repeated to yield 3.9 g (100%) of a crystalline solid with an acrid, toasted odor and a melting point of 122–124 °C (dec). The proton NMR spectrum at an ambient pH of 4.0 (300 MHz, D<sub>2</sub>O, DSS reference) showed 3.89 ppm (t, 6.7, 2 H), 3.4 (s, 6 H), 2.88 ppm (t, 6.7, 2 H). The carbon spectrum at an ambient pH of 4.0 (75 MHz, D<sub>2</sub>O, coaxial insert CHCl<sub>3</sub> reference) showed 176.6, 65.5, 56.0, 30.9 ppm.

**Sample Preparation.** NMR samples of 3-(dimethylazinoyl)propanoic acid (DMAPA) in D<sub>2</sub>O, deuterated methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, ethylene carbonate, dimethyl sulfoxide, and acetonitrile were prepared at 0.05 M for conforma-

(27) A reviewer has also noted that ion pairing between the carboxylate and the tetrabutylammonium counterion can also contribute to the stabilization of the gauche conformer.

(28) (a) Posner, T. *C. Berichte* **1905**, 38, 2316–2325. (b) Harries, C. D. *C. Berichte* **1899**, 32, 1315–1320.

tional analysis. For pH studies in D<sub>2</sub>O sample concentrations were in the range of 0.5–0.7 M. The pH was adjusted, with the aid of a glass electrode, from pH 0 to 4.3 using dilute DCl and for pH 4.4 to 10.0 with dilute NaOD.

To prepare the conjugate acid of DMAPA, one drop of trifluoroacetic acid was added to a prepared sample of the neutral species in water and aprotic solvents. The acidity of the solution was verified by pH meter, showing a pH near 1.0. The conjugate base was prepared by dissolving DMAPA and 2.0 equiv of tetrabutylammonium cyanide in ethanol and then removing the hydrogen cyanide and ethanol at reduced pressure. The resulting conjugate base was taken up in each deuterated solvent.

**Spectral Acquisition.** The <sup>1</sup>H NMR spectra for all protic solvents, DMSO, and acetonitrile samples were acquired at ambient temperature with either a 300 or a 600 MHz NMR spectrometer with signal lock on the deuterated solvent. Samples prepared with ethylene carbonate were heated to 38 °C to ensure that the solvent was liquid before spectral acquisition. The <sup>1</sup>H and <sup>13</sup>C NMR peaks were referenced to known chemical-shift positions of the alcohols and/or TMS.

**Determination of  $\lambda$  for the Carboxyl and Amine Oxide Substituents.** The coupling constant derived from the vicinal ethyl proton coupling of propanoic acid in all protic and aprotic solvents afforded  $\lambda$  values for the carboxyl group, which were found to be 0.39, independent of solvent, as also reported by Altona for CDCl<sub>3</sub> and D<sub>2</sub>O.<sup>11</sup> For determination of  $\lambda$  for the carboxylate group, tetrabutylammonium propionate was prepared by mixing propanoic acid with sodium hydroxide solution until a neutral pH, greater than its pK<sub>a</sub> of 4.88, was reached, indicating greater than 99% ionization. One equivalent of tetrabutylammonium bromide dissolved in ethanol was then added, and the mixture evaporated to dryness under reduced pressure to remove excess ethanol. One drop of the mixture was added to 0.75 mL of the deuterated solvents, water, methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, ethylene carbonate, dimethyl sulfoxide, and acetonitrile. The resulting mixtures were then filtered to remove the residual solid

sodium bromide. The vicinal ethyl proton–proton coupling constants, obtained at 300 MHz, were converted to  $\lambda$  values for the carboxylate substituent. The values showed greater variability than those of the carboxylic acid, being 0.44 in water; 0.43 in dimethyl sulfoxide, ethylene carbonate, and acetonitrile; and 0.35 in methanol, ethanol, isopropyl alcohol, and *tert*-butyl alcohol. A  $\lambda$  value of 0.29 for the carboxylate group in water is reported by Altona.<sup>11</sup> The  $\lambda$  values used for the amine oxide substituent in the protic solvents D<sub>2</sub>O, methanol, ethanol, isopropyl alcohol, and *tert*-butyl alcohol were as previously reported.<sup>2</sup> The  $\lambda$  values of the amine oxide substituent in aprotic solvents were 1.01 in ethylene carbonate, 1.09 in dimethyl sulfoxide, and 1.03 in acetonitrile.

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**Supporting Information Available:** Characterization, computational data, and Altona equations used for the calculations of percent gauche of DMAPA in protic and aprotic solvents. Also included is the unpublished research by P.V. Jog.<sup>2</sup> This material is available free of charge via the Internet at <http://pubs.acs.org>.

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