Conformational Preferences of \(N,N\)-Dimethylsuccinamate as a Function of Alkali and Alkaline Earth Metal Salts: Experimental Studies in DMSO and Water As Determined by \(^1\)H NMR Spectroscopy

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Supporting Information

**ABSTRACT:** The fraction of gauche conformers of \(N,N\)-dimethylsuccinamic acid (1) and its \(\text{Li}^+\), \(\text{Na}^+\), \(\text{K}^+\), \(\text{Mg}^{2+}\), \(\text{Ca}^{2+}\), and \(\text{N}(\text{Bu})_4^+\) salts were estimated in DMSO and \(\text{D}_2\text{O}\) solution by comparing the experimental vicinal proton−proton couplings determined by \(^1\)H NMR spectroscopy with those calculated using the Haasnoot, de Leeuw, and Altona (HLA) equation. In DMSO, the gauche preferences were found to increase with decreasing Ahrens ionic radius of the metal counterion. The same trend was not seen in \(\text{D}_2\text{O}\), where the gauche fraction for all of the metallic salts were estimated to be approximately statistical or less. This highlights the importance of metal chelation on the conformation of organic molecules in polar aprotic media, which has implications for protein folding.

**INTRODUCTION**

Metal ions interactions are crucial for many biological processes including protein folding, enzymatic catalysis, and signal transduction. One of the important roles of metal cations in biological system is the maintenance of precise electrochemical gradients across cell membranes. Such electrochemical gradients have been studied extensively in essential biological mechanisms such as nutrients transport and the maintenance of resting and action potentials. However, many studies have also demonstrated that conformational changes caused by metal chelation can alter the biological activities of substances. For example, \(\text{Mg}^{2+}\) and \(\text{Ca}^{2+}\) can induce distinct and separate conformational changes in calcium-binding protein 1, increasing structural stability of the protein. In addition, the mechanism involved in muscle contraction is initiated by the complexation of \(\text{Ca}^{2+}\) to calmodulin that is activated by concomitant conformational changes. Also, the binding of \(\text{Mg}^{2+}\) to three aspartic acid residues in CheY, a signal transduction protein in bacteria, facilitates activation of the protein.

Investigation of metal-induced conformational changes at the molecular level within biological systems is often complicated by other competing forces such as hydrogen bonds. Therefore, it is much more convenient to study simpler model systems, where a specific interaction of interest can be isolated. For example, Juaristi et al. used a 5-carboxy-1,3-dioxane derivative to show that LiBr is capable of disrupting intramolecular amide hydrogen bonds through the formation of a six-membered ring LiBr complex. A subsequent extension of Juaristi’s study using 5-carboxy-1,3-dioxanes revealed an increase in the stability of the axial isomer with \(\text{Ag}^+\) and \(\text{Li}^+\) salts, while larger metal ions such as \(\text{Na}^+\) and \(\text{K}^+\) had only marginal effects. In a recent paper, Roberts et al. examined the conformational preferences of \(N,N\)-dimethylsuccinamic acid (1, DMSA), its tetrabutylammonium salt (1e), and its lithium salt (1a). Interestingly, 1a resulted in an overwhelming preference for the gauche conformer (Figure 1) in aprotic solvents, while 1e remained predominantly trans (anti). The un-ionized 1

![Figure 1. Conformational equilibria of \(N,N\)-dimethylsuccinamic acid (1, top) and its lithium salt (1a, bottom) in DMSO.](image-url)
was determined to have a statistical gauche fraction of 0.66, indicating no preference for either the gauche or trans conformers. The conformational equilibrium of 1a were found to be strongly solvent-dependent, such that the solvents’ hydrogen bonding strength as measured by Kamlet–Taft’s α scale was a dominant factor.10

In this paper, the conformational study of 1 has been extended by including the Na+, K+, Mg2+, and Ca2+ salts. N,N-Dimethylsuccinamic acid (1) is particularly suitable for mimicking metal chelation in biological systems because both the carboxylate and amide metal complexes are commonly found in polypeptides.11 The motivation behind this work is to draw parallels between the conformational preferences of 1 as a function of these salts in DMSO and water as solvents. While water as a solvent imitates the aqueous environments commonly found in biological systems, DMSO mimics the polar aprotic media found in the interior of folded polypeptides.

RESULTS AND DISCUSSIONS

Model System. Simple 1,2-disubstituted ethane systems such as N,N-dimethylsuccinamic acid (1) are efficient models to study intramolecular interactions because they adopt well resolved gauche and trans conformers (Figure 2), where intramolecular noncovalent interactions can stabilize the gauche conformations. Because there are two possible gauche and one trans staggered conformers, the preference for each conformer can be deduced by measuring the ratios of their respective populations using proton (1H) NMR spectroscopy. In the absence of any preferential stabilization, the statistical gauche fraction (Fg) should be 0.67. Therefore, an Fg value greater than 0.67 indicates stabilization of the gauche conformer, plausibly by intramolecular interaction. On the other hand, Fg values less than 0.67 suggest an antagonistic relationship between the two substituents on the ethane, which may be due to electrostatic and/or steric repulsions.

The gauche fraction of each conformer was estimated by comparing the experimental vicinal proton coupling constants (JHH) measured by 1H NMR spectroscopy with their semiempirical counterparts calculated using the Haasnoot, de Leeuw and Altona (HLA) equation (eq 2).12 Equation 2 is an improved version of the original equation.13 Because the rotation about the “CH2−CH2” bond is rapid at room temperature, the experimental vicinal coupling constants (JHH) represent weighted averages of the individual couplings for the gauche and trans conformers, as described by eq 1. Note here that sum of the fractions is unity, i.e., Fg + Ft = 1. Also note that two experimental JHH values, i.e., J13 and J14 (where J13 = J14 = JH and J14 = JJ13) can be used to provide independent values for Fg and Ft.

\[ J_{1H}(\text{obs}) = \sum F_j \left( J_{1H}(e) \times F_j \right) + \left( J_{1H}(i) \times F_i \right) \]  

\[ J_{1H}(\text{semiempirical}) = 14.63 \cos^2 \theta_{ij} - 0.78 \cos \theta_{ij} + 0.60 \] 

Figure 2. Two possible gauche (g+) and trans (t−) conformers of N,N-dimethylsuccinamic acid, where M+ represents the alkali ions (Li+, Na+, and K+) and alkaline earth ions (Mg2+ and Ca2+). The various geometries were deduced from computational modeling (vide infra) in the gas phase.

Figure 3. DFT-optimized structures for the gauche (top) and trans (middle) conformers of 1a–1c and gauche (bottom) conformers of 1d–1e at the B3LYP/6-31+G(d,2p) level of theory in the gas phase. The calculated metal–oxygen distances are in Å, and the shown dihedral angles are in deg. Ahrens ionic radii were used to illustrate the metal ions.
calculated Li$^+\text{-}O$ distances for 1a (1.93–1.96 Å) in the gauche conformer are consistent with the values of 1.90–2.67 Å found in lithium-carboxylate X-ray crystal structures, while the values of 1.84–1.85 Å observed in the trans conformer appear to be slightly underestimated. The calculated Na$^+\text{-}O$ distances (2.26–2.29 Å) in gauche 1b and the K$^+\text{-}O$ distance in gauche 1c (2.58–2.70 Å) matched the values observed in crystal structures (i.e., 2.26–2.67 Å and 2.36–2.73 Å, respectively), whereas the values in the trans conformers are slightly lower (i.e., 2.19–2.20 Å for 1b and 2.53–2.54 Å for 1c). As for the divalent metal salts, the calculated Ca$^{2+}\text{-}O$ distances (2.41–2.45 Å) in 1d are within range of values found in crystal structures (2.26–2.59 Å). The calculated Mg$^{2+}\text{-}O$ distances (2.10–2.18 Å) however, are slightly greater than the values found in crystal structures (1.99–2.09 Å), which could be a result of differential packing forces in the solid state.

Interestingly, the calculated lowest-energy gauche conformers for 1b and 1c were similar to that previously calculated for the lithium salt (1a) in the sense that the metal ions preferred to bridge the carboxylate and amide oxygen atoms. The gauche conformers are more stable than their trans counterparts for every case. The calculated free energy of the gauche conformer of 1a is 3.8 kcal/mol more stable than the trans conformer. On the other hand, the gauche conformer of the sodium salt (1b) was calculated to be only 1.4 kcal/mol more stable than the trans conformer, while the calculated gauche/trans energy difference is 1.6 kcal/mol for the potassium salt (1b). Free energies of all the DFT gas phase optimized structures can be found in the Supporting Information.

Efforts were also made to investigate the possibility of an alternative gauche geometry, that is, where only one of the carboxylate oxygen atoms coordinates to the metal ions. However, the calculations produced gauche conformers of relatively higher energy than previously calculated. Other conformational possibilities for 1a–1c may involve aggregation, particularly for 1a. Lithium salts are known to form dimers, tetratetramers and higher-order aggregates. However, molecular mechanics calculations showed that, even in such aggregates (dimer and tetramer, for example), both the gauche and trans conformers can still exist. The differences in the gauche structures calculated for the monovalent metal salts (1a–1c) were, however, noticeable in the calculated dihedral angles. For example, of the three alkali metal salts, 1a had the smallest $\varphi_g$ value of 49.4$^\circ$, and 1c had the largest value of 60.8$^\circ$. It is reasonable to suggest that as the Ahrens ionic radius of the metal counterion increases, the dihedral angle widens in order to snugly accommodate the metal ions. Note that these angles are smaller than the value of 76.7$^\circ$ calculated for the un-ionized 1, where “weak” hydrogen bond has been suggested as the only stabilizing mechanism for the gauche conformer.

Unlike 1a–1c, the DFT gas phase optimized structure of divalent alkaline earth metal salts (1d–1e) share a single metal cation between two molecules of N$_2$N-dimethylsuccinamate. The divalent metal cation coordinates to six oxygen atoms, forming a very distorted octahedral geometry, as shown in Figure 3. A randomized conformational search by molecular mechanics calculations for the divalent metal salts did not find any conformers in which N$_2$N-dimethylsuccinamate adopted the trans conformation, which is not surprising considering the higher valency of Mg$^{2+}$ and Ca$^{2+}$ as well as their stronger chelation to the amide relative to the alkali metals. Synonymous to the trend observed for the alkali metal salts, $\varphi_g$ also increases with increasing Ahrens ionic radii for 1d and 1e, where 1d has a smaller calculated $\varphi_g$ of 46.9$^\circ$ and 51.3$^\circ$ for 1e.

The calculated dihedral angles were used to estimate gauche fractions of 1a–1e in DMSO solution. In aqueous solvents, however, one would expect that both the carboxylate and metal cation would be strongly solvated by water molecules, which should result in the complete dissociation of the ion pairs. Because hydrated metal ions have larger ionic radii, it is reasonable to assume that the actual $\varphi_g$ in aqueous solution should be greater than the calculated angles for 1a–1e. Furthermore, explicit solvent–solute hydrogen bond interactions in D$_2$O are often poorly captured by the current continuum solvation model (such as the IEFPCM and CPCM) employed by DFT calculations in the gas phase. For practical purposes, the $\varphi_g$ for measurements in aqueous solution was assumed to be 60$^\circ$ while the trans angle to be 180$^\circ$.

**Experimental $^1$J$_{HH}$ Coupling Constants.** With the calculated dihedral angles in hand, the next task is to determine the $J_{HH}$ experimental $^1$J$_{HH}$ coupling constants. NMR simulation software (gNMR 5.0) was used to iteratively reproduce the experimental $^1$H NMR spectra of the methylene protons region. Such simulations are essential because they provide an accurate depiction of the “real” coupling constants using 4-spin, AA’XX’ systems. The chemical shifts for the methylene protons are different for all the salts prepared, however, their spin–spin splitting appeared as doublet of triplets (Figure 4).

**Conformational Analysis.** Using the vicinal proton–proton coupling constants obtained from simulation of the experimental $^1$H NMR spectra and the dihedral angles from DFT gas phase calculations, the respective $F_g$ values for 1a–e were estimated as discussed earlier (Table 1 and 2). Compared to the un-ionized 1, which has a small gauche fraction of 0.66 ± 0.01, the metal salts generally showed higher gauche fraction in DMSO. The relatively small gauche fraction estimated for 1 in DMSO is likely the result of the carboxylic acid’s unfavorable

**Figure 4.** Stacked spectra of DMSA (1, top), its tetrabutylammonium salt (1f, middle), and its lithium salt (1a, bottom) in D$_2$O, spectral unit recorded in ppm.
Table 1. Experimental Vicinal H–H Couplings for the N,N-Dimethylsuccinamic Acid Salts (1a–1e) in DMSO and D_{2}O, Measured in Units of Hz

| solvents | Li^{+} salt 1a | Na^{+} salt 1b | K^{+} salt 1c | Mg^{2+} salt 1d | Ca^{2+} salt 1e |
|----------|---------------|----------------|----------------|----------------|----------------|
|          | J_{13}        | J_{14}         | J_{13}         | J_{14}         | J_{13}         |
| DMSO     | 6.02          | 8.13           | 6.64           | 7.75           | 6.64           |
|          | 6.64          | 8.36           | 6.08           | 8.18           | 7.29           |
|          | 7.04          | 7.94           | 7.28           | 7.31           | 6.36           |
| D_{2}O   | 6.59          | 8.33           | 7.08           | 7.35           | 6.64           |
|          | 7.04          | 7.94           | 7.28           | 7.31           | 6.36           |

"Data obtained from ref 10.

Table 2. Estimated Fraction Gauche (F_{g}) for the N,N-Dimethylsuccinamic Acid Salts (1a–1e) and the Ahrens Ionic Radii (\textbf{Å}) of the Metal Counter Ions^a

| solvent | Li^{+} salt 1a | Na^{+} salt 1b | K^{+} salt 1c | Mg^{2+} salt 1d | Ca^{2+} salt 1e |
|---------|---------------|----------------|----------------|----------------|----------------|
| DMSO    | 0.55 ± 0.01   | 0.55 ± 0.01    | 0.99 ± 0.04    | 0.53 ± 0.05    |
| D_{2}O  | 0.68          | 0.66           | 0.99           |

"The error in F_{g} is the deviation of using the J_{13} and J_{14} coupling constants for calculations. \(^{d}\)Data obtained from ref 10. \(^{c}\)Ahrens ionic radii were obtained from ref 28. \(^{e}\)F_{g} in DMSO was obtained assuming the dihedral angle to be 50°.

E configuration (Figure 5) that must be adopted in order to form an intramolecular hydrogen bond. \(^{32}\)

\[ \begin{align*}
\text{R} & \text{O} \\
\text{H} & \text{O} \\
\text{K} & \text{O} \\
\end{align*} \]

Figure 5. E and Z configurations of a carboxylic acid. Also see Figure 1.

In DMSO, the changing influence of the metal cation on the conformational preferences of N,N-dimethylsuccinamate is evident from the experimentally estimated gauche fractions of 1a–1e. Of the alkali metal salts, both the lithium and sodium salts (1a and 1b, respectively) showed preferences for the gauche conformer. 1a has the higher gauche fraction of 1.00, followed by 0.78 for 1b. These estimated gauche preferences are in agreement with DFT gas phase calculations, which predicted the gauche conformer to be more stable in both cases. DFT gas phase calculations also estimated the energy difference between the gauche and trans conformer of the lithium salt to be the highest among all the alkali metal salts, hence 1a’s relatively high gauche preference. The potassium salt (1c) on the other hand, has a much lower gauche fraction of 0.55 in DMSO, which suggests that 1c prefers the trans conformer. As for the alkaline earth metal ions, both the magnesium and calcium salts (1d and 1e, respectively) have relatively high preferences for the gauche conformer in DMSO. For 1d, when the DFT calculated \(\phi_{g}\) was used for the estimation of the gauche fraction, a value of 1.07 ± 0.05 was obtained. This is likely due to the underestimation of \(\phi_{g}\) by DFT gas phase calculations, as adjusting the \(\phi_{g}\) to 50° yielded a gauche fraction of 0.99 ± 0.04.

The calculated gauche fractions for the metal salts (1a–1e) are shown schematically in Figure 6 as a function of the Ahrens ionic radius of the metal counterion. For the metal salts in DMSO, it is apparent that gauche fractions of the salts decrease with increasing Ahrens ionic radii of the metal counterion. Metal cations with smaller Ahrens ionic radii are likely to fit better between the amide oxygen atom and carboxylate to bridge the two functional groups and induce gauche preference in N,N-dimethylsuccinamate. This assertion is supported by the DFT calculation results shown in Figure 3, where metal counters with smaller Ahrens ionic radii resulted in shorter metal–oxygen distances and smaller dihedral angles. In the case of 1c, K\(^{+}\) is likely too large to allow a proper fit between the amide and carboxylate.

In D_{2}O however, the interaction between N,N-dimethylsuccinamate and metal cations appears significantly different. No noticeable correlation between the Ahrens ionic radius of the metal counterion and gauche fraction of the N,N-dimethylsuccinamate could be established. For the metallic salts in D_{2}O, there is generally a lower gauche preference than in DMSO. In fact, none of the N,N-dimethylsuccinamate salts investigated have gauche fractions significantly higher than the statistical value of 0.67. The lack of gauche preferences in aqueous solution can be explained by the solvation efficiency of water. Water molecules can isolate and solvate cations (metal cation) and anions (carboxylates) appreciably well. Such isolated solvation would greatly diminish interactions between metal ions and N,N-dimethylsuccinamate. Previous study also found that 1a has a lower gauche fraction in solvents with better hydrogen donor propensities, which are also solvents likely to solvate anions efficiently. \(^{10}\)
CONCLUSIONS

Using 1H NMR spectroscopy, we have demonstrated that the conformational equilibria of DMSA and its metal salts are strongly solvent dependent. In DMSO solution, as the Ahrens ionic radius of the metal counterion increases, the gauche fraction of N,N-dimethylsuccinamate decreases. Interestingly, DFT calculations strongly suggest that the gauche preferences of the metallic salts are caused by cationic bridging of the amide and carboxylate oxygen atoms. The same interaction is much weaker in D2O, where the estimated gauche fractions were significantly below the statistical 0.67 value. These results seem to suggest that metal chelation has an especially powerful influence on the conformation of organic molecules in polar aprotic media.

EXPERIMENTAL SECTION

Commercial N,N-dimethylsuccinic acid (1) of ∼98% purity was used without further purification. The Na+(1b) salt was prepared by treating 1 with an equivalent mole of NaH in THF. The K+(1c) salt was prepared by treating 1 with an equivalent mole of KCN. The Mg2+(1d) and Ca2+(1e) salts were prepared by treating 1 with 0.5 equiv of Mg(OH)2 and Ca(OH)2 respectively in water. Solvent was then evaporated and samples were dried in vacuo. Commercial DMSO-d6 and D2O were used without further purifications.

The 1H NMR spectra were taken with Varian 300, 400, and 600 MHz spectrometers at 25 °C. See Supporting Information for specific acquisition parameters of each sample.

ASSOCIATED CONTENT

Supporting Information

Experimental 1H NMR spectra and Cartesian coordinates of the optimized structures from DFT calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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