

Conformational Equilibria of *N,N*-Dimethylsuccinamic Acid and Its Lithium Salt as a Function of Solvent

Albert Tianxiang Liu, Bright U. Emenike, William R. Carroll, and John D. Roberts*

Gates and Crellin Laboratories of Chemistry, California Institute of Technology,
Pasadena, California 91125, United States

robertsj@caltech.edu

Received December 6, 2012

ABSTRACT



The conformational preferences of *N,N*-dimethylsuccinamic acid and its Li^+ salt were estimated by comparing the respective experimental NMR vicinal proton–proton coupling constants to semiempirical coupling constants for each staggered conformer as derived by the Haasnoot–De Leeuw–Altona method. The strong *gauche* preferences for the Li^+ salts clearly depended more on the solvents' hydrogen-bond donating strength (α) than on their hydrogen-bond accepting (β) counterpart, where α and β are the corresponding Kamlet–Taft parameters.

Simple 1,2-disubstituted ethane systems ($\text{XCH}_2\text{CH}_2\text{Y}$), with staggered conformers corresponding to *gauche* and *trans* conformational isomers, can provide insight into the intramolecular forces that stabilize functional groups. The conformational studies of small molecules with peptide subunits (amides) have been focused primarily on hydrogen bonding induced changes. As a result, there are numerous reports revealing the physical organic chemistry prerequisites for the formation of favorable hydrogen bonding interactions.^{1,2} In contrast, metal–ion chelations such as the Li^+ complex have received less attention, even though when fine-tuned, they can provide stronger stabilization. For example, Boger et al.³ noticed profound perturbation on the conformational equilibria of Bourvadins (bicyclic hexapeptides natural products) upon the addition of 1 equiv of lithium chloride.³ Also, peptide-based receptors that can selectively bind Li^+ in preference to other cations have been

designed previously.⁴ The addition of lithium chloride to a solution of Cyclosporin A, a drug widely used clinically to prevent graft rejection in organ or bone marrow transplantations, led to a drastic increase in *PPIase* (enzyme) inhibition through the formation of different Li^+ complexes depending on the lithium chloride concentration.⁵

In this research, the conformational preferences of *N,N*-dimethylsuccinamic acid (**1**) and its Li^+ and $\text{N}(\text{Bu})_4^+$ complexes (**2** and **3**, respectively) were estimated in different solvents by comparing the semiempirical constants for each conformer derived by the Haasnoot–De Leeuw–Altona (HLA) method⁶ to the time-averaged vicinal proton–proton coupling constants observed experimentally.

In order to obtain the population of each conformer (*gauche* and *trans*), the experimental coupling constants ($^3J_{\text{obs}}$) for $^3J_{13}$ and $^3J_{14}$, where $^3J_{23} = ^3J_{14}$ and $^3J_{24} = ^3J_{13}$, for **1**, **2**, and **3** were compared to their respective predicted (theoretical) values according to eq 1: F_g and F_t represent

(1) Perrin, C. L. *Acc. Chem. Res.* **2010**, *43*, 1550.

(2) Stasko, D.; Hoffmann, S. P.; Kim, K. C.; Fackler, N. L. P.; Larsen, A. S.; Drovetskaya, T.; Tham, F. S.; Reed, C. A.; Rickard, C. E. F.; Boyd, P. D. W.; Stoyanov, E. S. *J. Am. Chem. Soc.* **2002**, *124*, 13869.

(3) Boger, D. L.; Patane, M. A.; Zhou, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 7357.

(4) Furlan, R. L. E.; Ng, Y. F.; Otto, S.; Sanders, J. K. M. *J. Am. Chem. Soc.* **2001**, *123*, 8876.

(5) Kock, M.; Kessler, H.; Seebach, D.; Thaler, A. *J. Am. Chem. Soc.* **1992**, *114*, 2676.

(6) Altona, C.; Francke, R.; Dehaan, R.; Ippel, J. H.; Daalman, G. J.; Hoekzema, A.; Vanwijk, J. *Magn. Reson. Chem.* **1994**, *32*, 670.

the fractions of *gauche* and *trans* respectively.

$$J_{ij(\text{obs})} = J_{ij(\text{gauche})}F_g + J_{ij(\text{trans})}F_t \quad (1)$$

Note here $F_g + F_t = 1$. The theoretical $^3J_{13}$ and $^3J_{14}$ values were calculated according to Haasnoot–Altona's method⁶ (eq 2), where ϕ is the dihedral angle and λ_i is the empirical electronegativity variables for substituent groups.

$$^3J_{\text{HH}} = 14.63 \cos^2 \phi_{ij} - 0.78 \cos \phi_{ij} + 0.60 + \sum \lambda_i [0.34 - 2.31 \cos^2(\zeta_i \phi_{ij} + 18.4|\lambda_i|)] \quad (2)$$

The λ_i values for $-\text{CO}_2^-$, $-\text{CO}_2\text{H}$, and $-\text{CONMe}_2$ functional groups were those provided by Altona and co-workers.⁷ The parameter ζ_i can be +1 or –1 depending on the relative orientation of the substituent i . The essential dihedral angles (ϕ) for the *gauche* and *trans* conformers were derived from the optimized structures using the B3LYP/6-31+G(2d,2p) level of computational theory.⁸ The alternative to the computational approach is to assume that the dihedral angles were idealized (perfectly staggered), i.e. 60° (ϕ_g) and 180° (ϕ_t) for *gauche* and *trans* angles, respectively. However, such assumptions often overestimate the percentage of *gauche* conformers.^{9,10} The graphical representation of the optimized structures is shown in Figure 1.

To account for solvation effects in our computational modeling, the *integral equation formalism polarizable continuum model* (IEF–PCM) option of the Gaussian program was used.⁸ However, no significant changes were noticed in the dihedral angles with solvent variation.

For **1**, ϕ_g was calculated to be 76.7° ; this value is similar to $74(\pm 4)^\circ$ experimentally obtained for succinate (monoanion) in liquid crystal media.¹¹ In the case of **2**, ϕ_g was calculated to be much smaller (49.5°)

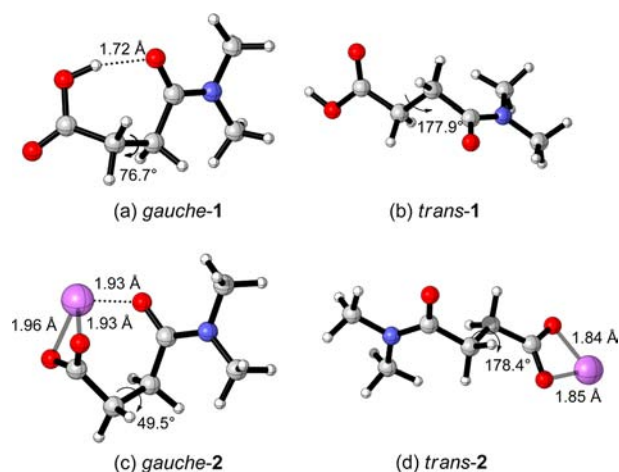


Figure 1. DFT-optimized structures for the *gauche* and *trans* conformers of **1** and **2** using the B3LYP/6-31+G(2d,2p) level of theory in the gas phase.

(7) Altona, C.; Ippel, J. H.; Hoekzema, A.; Erkelens, C.; Groesbeek, M.; Donders, L. A. *Magn. Reson. Chem.* **1989**, *27*, 564.

(8) Rummey, J. M.; Boyce, M. C. *J. Chem. Educ.* **2004**, *81*, 762.

The symmetrical placement of the Li^+ between the two carboxylate oxygens meant that a contracted ϕ_g was required to yield a compact *gauche* conformation (shown in Figure 1c). The calculated Li–O distances found for *gauche-2* (1.93–1.96 Å, Figure 1c) are within the experimental bond lengths (1.90–2.67 Å) observed in X-ray crystal structures.^{12,13} However, for *trans-2* (Figure 1d), the value of ~ 1.85 Å appears somewhat underestimated by this level of computation. In addition, aggregate formations, which are prominent in solid state structures, were not considered in the solution-based computational modeling.

Table 1. Measured Vicinal ^1H – ^1H Coupling Constants for *N,N*-Dimethylsuccinamic Acid and Its Li^+ and $\text{N}(\text{Bu})_4^+$ Salts in a Selection of Deuterated Protic and Aprotic Solvents

solvent	DMSA 1		Li^+ Salt 2		$\text{N}(\text{Bu})_4^+$ Salt 3	
	$^3J_{13}$	$^3J_{14}$	$^3J_{13}$	$^3J_{14}$	$^3J_{13}$	$^3J_{14}$
<i>Aprotic</i>						
CDCl_3	5.27	7.78	6.16	7.99	6.22	9.20
DMSO	5.55	7.70	6.02	8.13	6.03	9.31
Acetone	5.55	7.74	4.63	7.99	6.16	9.40
MeCN	5.25	7.51	5.38	8.15	6.45	8.56
<i>Protic</i>						
D_2O	5.51	7.65	6.59	8.33	6.49	8.48
MeOD	5.61	7.65	6.31	8.84	6.22	9.28
EtOD	5.85	7.67	6.89	8.24	5.86	10.00
<i>i</i> -PrOD	6.47	7.19	6.86	7.17	5.73	10.45

Table 2. Equilibrium *Gauche* Fraction (F_g) of *N,N*-Dimethylsuccinamic Acid and Its Li^+ and $\text{N}(\text{Bu})_4^+$ Salts in a Selection of Deuterated Protic and Aprotic Solvents

solvent	α^a		β^a		DMSA (1)		Li^+ salt (2)		$\text{N}(\text{Bu})_4^+$ salt (3)	
	F_g	\pm^b	F_g	\pm^b	F_g	\pm^b	F_g	\pm^b	F_g	\pm^b
<i>Aprotic</i>										
CDCl_3	0.20	0.10	0.68	0.02	0.98	0.02	0.39	0.01		
DMSO	0.00	0.76	0.66	0.01	1.00	0.03	0.37	0.02		
Acetone	0.08	0.43	0.66	0.01	1.03	0.06	0.38	0.01		
MeCN	0.15	0.40	0.66	0.03	1.05	0.04	0.44	0.01		
<i>Protic</i>										
D_2O	1.17	0.47	0.64	0.04	0.68	0.03	0.44	0.02		
MeOD	0.98	0.66	0.64	0.01	0.62	0.03	0.39	0.01		
EtOD	0.86	0.75	0.64	0.01	0.72	0.02	0.33	0.02		
<i>i</i> -PrOD	0.80	0.84	0.58	0.02	0.84	0.05	0.31	0.01		

^a Obtained from ref 13. ^b The \pm columns represent the deviation of *gauche* fraction calculated from J_{13} and J_{14} coupling constants.

(9) Kent, D. R.; Petterson, K. A.; Gregoire, F.; Snyder-Frey, E.; Hanely, L. J.; Muller, R. P.; Goddard, W. A.; Roberts, J. D. *J. Am. Chem. Soc.* **2002**, *124*, 4481.

(10) Price, D. J.; Roberts, J. D.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1998**, *120*, 9672.

(11) Smith, A. A.; Drake, M. D.; Rahim, A. K.; Roberts, J. D. *J. Phys. Chem. A* **2008**, *112*, 12367.

(12) Fleck, M.; Schwendtner, K.; Hensler, A. *Acta Crystallogr.* **2006**, *C62*, m122.

(13) Wiesbrock, F.; Schmidbaur, H. *J. Chem. Soc., Dalton Trans.* **2002**, 4703.

For both **1** and **2**, ϕ_t was calculated to be $\sim 178^\circ$ (177.9° for **1**; and 178.4° for **2**). Unfortunately, no *gauche* conformation could be modeled for **3** because the resulting optimized structures in modeling both the *gauche* and the *trans* conformers produced the same low-energy structure with identical geometry.

In this case, for practical purposes, we assumed that $\phi_g = 60^\circ$ and $\phi_t = 180^\circ$. Table 1 shows the experimental ^1H – ^1H vicinal coupling constants for **1**, **2**, and **3**.

With the dihedral angles and coupling constants in hand, the next task is to establish the population of each conformer. Because there are two possible *gauche* conformers and one *trans* conformer around the single “ $\text{CH}_2\text{--CH}_2$ ” bond of simple ethane systems, an F_g of 0.67 is the statistical value that reflects no conformational preferences. An $F_g > 0.67$ indicates a preference for the *gauche* conformer, while an $F_g < 0.67$ means the *trans* isomer is preferred instead. For Li^+ complex **2**, there is a notable conformational change associated with solvent hydrogen-bond strength because F_g was greater than 0.67 in all the solvents except for methanol (Table 2). In aprotic solvents, the Li^+ complex (**2**) displayed *gauche* preferences greater than 99% ($F_g = 1.02 \pm 0.03$, average of four solvents), but this value drops in the protic solvents to a maximum of 0.84 ± 0.05 in 2-propanol and a minimum of 0.62 ± 0.03 in methanol.

Surprisingly, **3** showed no preference for the *gauche* conformer in any of the solvents used. In fact, F_g did not exceed 0.44, which indicates the dominance of the *trans* isomer. Why would different cation counterions cause a profound change on the conformational preferences of the anion of **1**? In light of the apparent solvent effect, one possible explanation to rationalize the observed trend is the solute and solvent interactions. It appears that the bulky $^+\text{N}(\text{Bu})_4$ counterion in **3** might be expected to form a weaker complex with the carboxylate anion than Li^+ in **2**. As a result, **3** might be easily solvated through solute–solvent hydrogen-bonding interactions involving the carboxylate anion, where the solvent is a protic hydrogen-bonding donor. The solvation of the ‘free’ carboxylate through hydrogen bonding should favor the *trans* conformer because solvent molecules can access the carboxylate anion more readily in this form than in the *gauche* isomer. Furthermore, given the relative small size of Li^+ , it appears as though Li^+ could fit snugly between the oxygens of the carboxylate while chelating to the amide oxygen’s lone pair in a Lewis acid fashion (Figure 1c). This arrangement should enable the positive charge on Li^+ to be delocalized onto the oxygen and stabilize the *gauche* conformation in the process.

The α and β Kamlet–Taft solvent parameters^{14,15} are useful for quantifying hydrogen-bond donating and accepting strengths of solvents, respectively. Only solvents with hydrogen-bond donating abilities are capable of solvating the carboxylate anion, thereby, disrupting the

preference for *gauche*, as in the case of protic solvents. Our data for **2** show a roughly linear correlation for the plot between F_g and α values ($R^2 = 0.90$), but not for the F_g and β plot ($R^2 = 0.16$) (Figure 2). These results give credence to the notion that solute–solvent hydrogen bonding interactions play an important role in the conformational equilibrium of the ionized species (**2** and **3**). The preference for *gauche* can be directly related to the solvents’ α -values through the linear equation: $F_g = 1.05 - 0.35\alpha$ derived from the plot (Figure 2). Other solvent parameters, such as polarity ($E_T(30)$) and dielectric constants (ϵ), did not provide reasonable trends.

In the case of **1**, only the statistical F_g values (~ 0.67) were observed with aprotic solvents. It is worth mentioning that computational modeling in the gas phase predicted the *gauche* isomer of **1** (Figure 1a) to be 2.55 kcal/mol more stable than the *trans* isomer (Figure 1b).

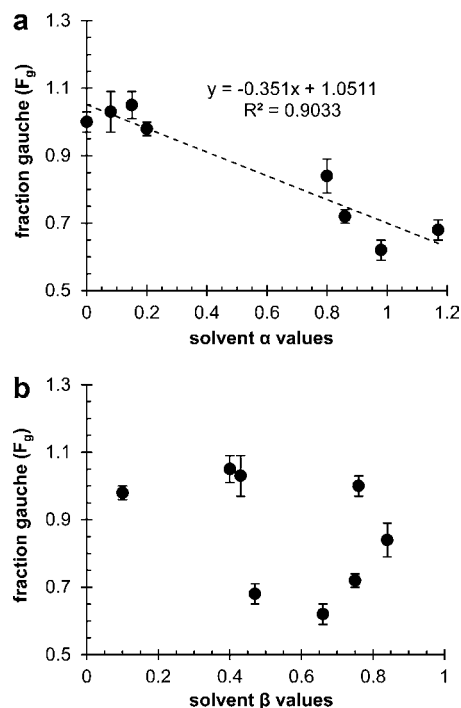


Figure 2. (a) Comparison of Kamlet–Taft solvent parameters (α) and fraction of *gauche* (F_g). (b) Comparison of Kamlet–Taft solvent parameters (β) and fraction of *gauche* (F_g).

However, no such preference was noticed in the NMR solution experiment. In protic solvents, where no intramolecular hydrogen bond is expected, F_g values were, however, slightly lower than statistical values (0.64–0.58). This small change suggests that the strength of the intramolecular hydrogen bonding that may or may not be present was too weak to cause a noticeable conformational preference. The inconsistency between the computed relative energies and the lack of *gauche* preference from the experimental result could stem from the fact that computational modeling generally underestimates stabilization due to intermolecular interactions.

(14) Lagalante, A. F.; Jacobson, R. J.; Bruno, T. J. *J. Org. Chem.* **1996**, *61*, 6404.

(15) Taft, R. W.; Pienta, N. J.; Kamlet, M. J.; Arnett, E. M. *J. Org. Chem.* **1981**, *46*, 661.

In summary, although Li^+ has been known to induce conformational changes in organic molecules, this study represents an interesting example of isolating the effect of various protic and aprotic solvents. We have shown here that the solvent's hydrogen-bond donor propensity (α) was more important than the hydrogen-bond acceptor counterpart's propensity (β).

Acknowledgment. We thank the National Science Foundation under Grants CHE-0543620, TG-CHE1000106 and the donors of the Petroleum Research Fund administered by the American Chemical Society for support for this research. Other important support came from the Summer Undergraduate Research Fellowship Program (SURF) at the California Institute of Technology, the Senior Scientist Mentor Program of the Camille and

Henry Dreyfus Foundation, and the NORAC grant of Dr. and Mrs. Chester M. McCloskey. We are indebted to Merck and Company, Dr. David J. Mathre, and Edith M. Roberts for their helpful financial assistance. The facilities of the MCS used in these studies were established with grants from DURIP-ONR and DURIP-ARO, with additional support from ONR, ARO, NSF, NIH, DOE, Chevron, Nissan, Dow Corning, Intel, Pfizer, Boehringer-Ingelheim, and Sanofi-Aventis.

Supporting Information Available. Experimental spectra and Cartesian coordinates of the optimized structures from the theoretical calculations. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.