Conformational Analysis of 3-(Trimethylsilyl)propionic Acid by NMR Spectroscopy: An Unusual Expression of the β-Silyl Effect

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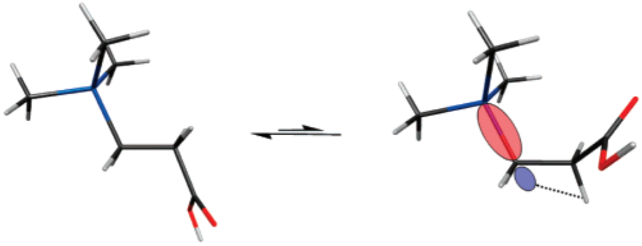


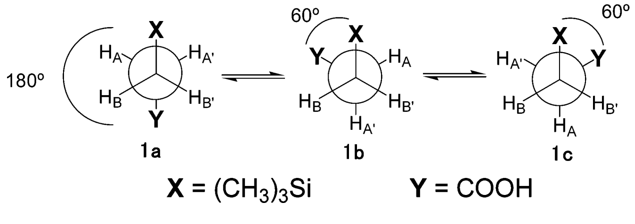
The rotational freedom of the carbon−carbon single bonds of 1,2-disubstituted ethanes affords the possibility of these compounds existing as a rapidly interconverting mixture of conformers in solution. The conformational preferences of one such compound, 3-(trimethylsilyl)propionic acid, and its anion were studied in water, dimethyl sulfoxide, methanol, ethanol, isopropyl alcohol, *tert*-butyl alcohol, tetrahydrofuran, and toluene with ^{1}H NMR spectroscopy. The conformational preferences were determined from the vicinal proton−proton coupling constants between the hydrogen nuclei of the CH_2CH_2 group with the aid of the Altona equations to derive the equilibrium anti and gauche percentages of rotamers from the averaged NMR−time scale couplings. Conformational analyses of 4,4-dimethylpentanoic acid and its anion as well as 2-(trimethylsilyl)ethanesulfonate anion were also conducted to compare the relative structural influences on the conformational preferences of silicon and carbon.

Introduction

Conformational equilibria are an essential part of understanding the structures and behavior of organic molecules. Many molecules exist as a mixture of multiple conformational isomers, as the result of rotations about carbon−carbon single bonds. The question of how conformations differ in energy and why some are preferred can be important in predicting structures and reactivities of larger molecules. The generally small energy differences between conformers mean that otherwise subtle interactions can produce observable effects.

Much research has attempted to describe and rationalize conformational preferences. Conformational analysis of 1,2-disubstituted ethanes has given many simple examples in which three rotational isomers result from preferred angles of rotation about the central carbon−carbon single bond. With achiral substituents, the preferred conformers for 1,2-disubstituted ethanes are the anti and two energetically equivalent, enantiomeric gauche configurations as depicted in Scheme 1. These arrangements rapidly interconvert in solution on time scales as short as 10^{-9} s.[1]

SCHEME 1. Minimum-Energy Rotational Isomers of a 1,2-Disubstituted Ethane: (a) Anti Conformer and (b, c) Enantiomeric Gauche Conformers



Previous work[2] in this area has included investigation of similar 1,2-disubstituted ethanes, such as 1,4-butanedioic acid in the conformational equilibria offered by the neutral, monoanionic, and dianionic states as a function of solvent in water, and in a series of protic and aprotic (incapable of acting as a hydrogen bond donor) solvents. In attempting to build on concepts developed in previous studies of conformational

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[2] Williams, L. N.; Petterson, K. A.; Roberts, J. D. *J. Phys. Chem. A* **2002**, *106*, 7491−7493.

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preferences, this project was aimed at examining the preferences of 1,2-disubstituted ethanes for which there is no prior conformational information: those of 3-(trimethylsilyl)propionic acid (TSPA) and its anion. Previous studies with similar silicon-containing compounds have been largely concerned with this element's particular influence on reactivity at carbocation centers.[3]

Silicon has a smaller electronegativity than carbon and hence is more electron donating, potentially allowing stabilization of cationic centers at the α, β, or γ position, relative to silicon. The β-effect of silicon shows the greatest enhancement of reactivity, because of the high polarizability of the carbon−silicon bond, making it particularly able to stabilize positive charge by hyperconjugation.[4] Studies comparing the acidity of $(CH_3)_3SiCH_2CO_2H$ with that of $(CH_3)_3CCH_2CO_2H$ also show the $(CH_3)_3Si$ substituent as more electron donating than $(CH_3)_3C$.[3] The γ-effect of silicon produces similar increases in reactivity, but in contrast, the α-effect causes decreases in reactivity, possibly because of poorer hyperconjugative stabilization of Si−C bonds by conjugation with the carbocation p-orbital.[5] We expected these effects might produce interactions capable of perturbing the distribution of anti and gauche conformations away from the statistical mixture. The possibility of some degree of complexation of an anionic carboxyl group with the silicon of the CH_3Si group was also considered and, as will be seen later, such an interaction is consistent with the results of gas-phase computations of the structure of the TSPA anion. However, it does not appear to be important for determining conformational preferences of the anion in solution.

Altona's modification of the Karplus equation[6] is widely used in determination of the conformational preferences. The Altona equation relates vicinal proton coupling constants ($^3J_{HH}$) to the $X-CH_2-CH_2-Y$ dihedral angle (φ) and an empirical electronegativity variable (λ), which can be determined for a given substituent X from the hydrogen couplings of CH_3CH_2X in particular solvents.[6] Previous studies[4] show that hyperconjugation follows a dependence on the dihedral angle. 1,2-Disubstituted cyclohexane systems used to study the β-effect of silicon at dihedral angles between the silicon substituent and a leaving group of 60° and 180° have shown that anti geometry is consistent with a dependence on vertical stabilization provided by the substituent X when its geometry or its distance from the carbon bonded to substituent Y remains constant as the C−Y bond is broken.[7] It has been suggested[5] in cyclohexanes and adamantanes that similar w-shaped alignment of bonds leads to overlap of the C−Si and C−Y backlobes, which may underlie the torsional dependence of the γ-effect when the Si−C−C−C dihedral is close to 180°. Although stannyl systems with dihedrals close to 0° have been studied, no such work appears to have been done on silyl compounds.[8] Because the dihedral angles in solution between the substituents are not specifically known for TSPA, it seems best to assume that the three-bond H−C−H dihedral angles have the staggered values of 60° and 180°. The Altona equation can then be used to calculate the coupling constants for the individual conformers.

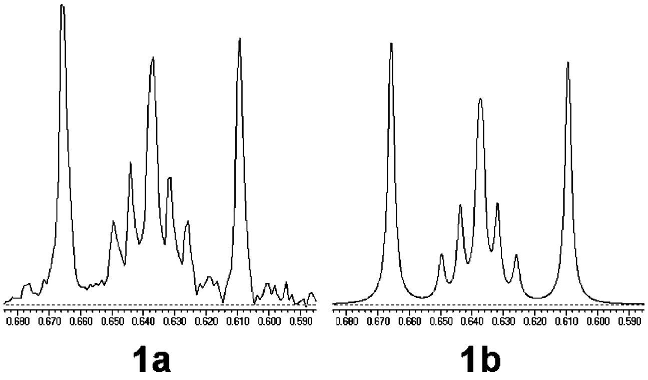

FIGURE 1. Comparison of ^1H NMR (D_2O, 300 MHz) spectra acquired (a) experimentally and (b) by gNMR simulation of the methylene α to the trimethylsilyl group.

The empirical electronegativity variable, λ, for the trimethylsilyl substituent has not been previously reported. It was determined that λ for the trimethylsilyl substituent does not vary with solvent and has a value of −0.37, indicating that the substituent is less electronegative than hydrogen with a reported λ value of −0.18.[6]

The experimental J values were obtained from the NMR spectra with the aid of gNMR 4.1[9] in which the proton−proton couplings are estimated and iteratively adjusted until a simulated spectrum is obtained that matches the experimental spectrum as shown in Figure 1. The conformational preferences of 3-(trimethylsilyl)propionic acid and its commercially available sodium salt (typically used as proton chemical-shift references in water) were estimated as well as those of the corresponding tetrabutylammonium salt.

In this project, conformational analyses were carried out for a series of protic and aprotic solvents, with the objective of improving our understanding of how hydrogen bonding, electrostatic repulsions, steric hindrance, solution environments, and other influences interact and affect conformational preferences.

Results and Discussion

As with other 1,2-disubstituted ethanes, the substituent-group characteristics are expected to influence the relative populations of the anti and gauche conformers in solution. Steric effects arising from the bulkiness of the trimethylsilyl substituent are especially likely to be expected to influence a substantial preference for the anti conformer.

The derived vicinal proton coupling constants for the central CH_2 resonances for TSPA and its anion in several protic and aprotic solvents are listed in Table 1. The assignment of the J_{13} and J_{14} designations can be reversed with no change in the simulated gNMR spectrum. However, when analyzed with the Altona procedure, two sets of gauche-to-anti conformer ratios are obtained.[10] These sets of results have different uncertainties in the calculated gauche−anti ratio. As an example, switching J_{13} and J_{14} of TSPA in D_2O results in a percent-gauche value of 100% with an uncertainty of ±17%. The large percent-gauche values and uncertainties could be obtained for the other solvents

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(9) *gNMR 4.1*, I; Adept Scientific: Litchworth, Herts, UK, 1999.

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TABLE 1. Measured Vicinal $^1H-^1H$ Coupling Constants for 3-(Trimethylsilyl)propionic Acid and Its Anion in a Selection of Protic and Aprotic Solvents

	acid, $^3J_{obs}$, Hz		anion, $^3J_{obs}$, Hz	
solvent	J_{13}	J_{14}	J_{13}	J_{14}
H_2O	5.9	11	5.7	11
MeOH	6.0	11	5.1	12
EtOH	5.5	11	5.0	13
i-PrOH	5.2	12	4.9	13
t-BuOH	4.5	12	4.3	13
DMSO	6.1	11	5.5	12
THF	5.7	11	5.0	12
toluene	5.8	11	5.2	12

TABLE 2. Calculated Equilibrium Percentages of the Gauche Conformer of 3-(Trimethylsilyl)propionic Acid and Its Anion in Solutions of Protic and Aprotic Solvents

		acid		anion	
solvent	dielectric constant	% gauche	± %	% gauche	± %
H_2O	78.5	38	4	34	5
MeOH	32.6	38	3	26	6
EtOH	24.3	32	6	23	5
i-PrOH	18.3	29	6	23	5
t-BuOH	12.1	20	9	15	8
DMSO	47.2	41	4	31	5
THF	7.52	35	5	24	5
toluene	2.40	36	4	26	4

as well. For this reason, the result with the lower magnitude uncertainty was always used.

The Altona equation has been previously verified[6] by comparison between the predicted and experimental couplings of compounds with known dihedral angles and has a standard deviation of 0.36 Hz. When experimental values for succinate monoanion in D_2O couplings are compared with predicted values from the Altona equation, assuming dihedral angles of 60° and 180°, the result matches what would be predicted from Westheimer and Benfey's[11] work that shows a lack of intramolecular hydrogen bonding, even in a supposedly favorable case such as the phthalate monoanion.

The estimated percentages of the gauche conformer of TSPA and its anion in solution for the selected solvents are shown in Table 2. The percent-gauche values for all of the solutions fall within a range of 20−38% for the acid and 15−34% for the anion. These data indicate that TSPA has a preference of 0.6−1.2 kcal/mol for the anti conformer of the acid and 0.8−1.1 kcal/mol for the anion. Given the likely substantial steric hindrance expected from the trimethylsilyl substituent of this compound, the result is not surprising.

Table 2 shows that preference for gauche conformers of the selected protic solvents both for TSPA and its anion correlates well with dielectric constants. Aprotic solvents follow the trend, except that THF and toluene give almost identical results, which at least correlate with the trend in smaller gauche percentages with decreasing dielectric constant.

No significant differences were found between tetrabutylammonium or sodium cations as counterions for the anion of TSPA. A comparison of TSPA to 4,4-dimethylpentanoic acid and its anion revealed significant differences in the role of carbon and silicon in determining conformational preferences as a function of solvent (compare Table 3 with Table 2).

TABLE 3. Calculated Equilibrium Percentage of the Gauche Conformer of 4,4-Dimethylpentanoic Acid and Its Anion in Solutions of Protic and Aprotic Solvents

		acid		anion	
solvent	dielectric constant	% gauche	± %	% gauche	± %
H_2O	78.5	31	2	31	2
MeOH	32.6	30	2	30	2
EtOH	24.3	30	2	31	2
i-PrOH	18.3	31	2	31	2
t-BuOH	12.1	31	2	31	2
DMSO	47.2	27	2	29	2
THF	7.52	26	2	29	2
toluene	2.40	28	2	26	2

TABLE 4. Calculated Equilibrium Percentage of the Gauche Conformer of the 2-(Trimethylsilyl)ethanesulfonate Anion in Solutions of Protic and Aprotic Solvents

		anion	
solvent	dielectric constant	% gauche	± %
H_2O	78.5	6	5
MeOH	32.6	6	5
EtOH	24.3	5	5
i-PrOH	18.3	5	5
t-BuOH	12.1	5	5
DMSO	47.2	15	5
THF	7.52	13	5
toluene	2.40	9	8

The gauche preferences for both 4,4-dimethylpentanoic acid and its anion fall within the narrow range of 26−31%. There are no apparent trends in the gauche percentages that parallel the aforementioned trends with TSPA and its anion between gauche preferences with dielectric constant.

The conformational preferences of the 2-(trimethylsilyl)ethanesulfonate anion are shown in Table 4.

The gauche values for all of the solutions used fall within a range of 5−15%. The tetrahedral sulfonate substituent enhances the steric interactions compared to planar carboxylate groups in the TSPA and 4,4-dimethylpentanoic acid and their anions, an effect documented previously in interactions of the sulfonate substituent and the carboxylate groups with the trimethylammonium substituent.[12]

When TSPA is compared with its anion, the anion shows a stronger preference for anti than the acid. This effect and the variation of gauche percentage with solvent polarity may indicate that the interactions with solvent or between trimethylsilyl and carboxyl or carboxylate stabilize the anti anion relative to the gauche form. Because the *tert*-butyl and silyl compounds show similar behavior in polar solutions, the silyl-specific effect is one that favors anti as polarity decreases rather than one that favors gauche in polar media. The possibility that a close association between carboxylate and the solvated counterions may be rendered less likely in that the sodium and tetrabutylammonium cations show similar conformational preferences in several solvents, so the formation of tight-ion pairs with sodium is not likely to account for the variations with solvent polarity.

In aprotic solvents of low polarity, gauche percentages are observed that do not follow the trend seen in alcohols of varying

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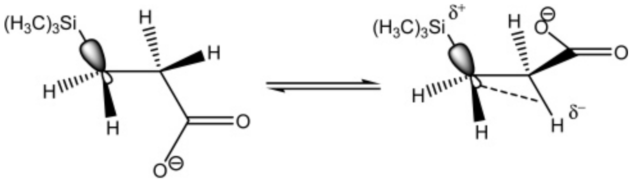
dielectric constant. The anomalous effects in THF and toluene could involve dimerization of the acid leading to a local polarity different from that of the bulk solvent. Carboxylic acids in aprotic solvents are known to strongly favor dimerization at concentrations used in this study.[13] The very small[14] increase in gauche preference of the anion in aprotic solvents over protic solvents of similar dielectric constant may be due to the complexation of the carboxylate to the silyl group. An analogous increase in nucleophilicity has been observed in changes of solvent from alcohols to ones less able to coordinate anions, such as DMF and DMSO.[15] These effects are commingled with the steric and other effects resulting in an overall anti preference modulated according to solvent polarity and protonation state that is not observed for the *tert*-butyl acid.

To determine the geometries of these compounds in the gas phase limiting case of apolar, aprotic media, computational studies on various conformers were undertaken in the gas phase at the B3LYP/6-31+G(d,p) level by using GAMESS.[16] The structure of the corresponding gauche *tert*-butyl acid was calculated at the same level of theory, and a number of interesting comparisons can be made. The gauche silyl acid had a C−C−C−Si dihedral of 67° while the *tert*-butyl compound was at 79°. The anti conformers were 177° and 172°, respectively. When these values were used in the Altona equation, the percent gauche values decreased slightly (compared to the dihedral angles of 60° and 180°); however, the overall trends observed in Tables 2 and 3 remained the same.

Hyperconjugative interactions affecting the C−H bonds α to the carboxylate were also computed. With the silyl acid, shifting from the gauche to anti conformation leads to a decrease in bond order for both C−H bonds α to the carboxyl. In the *tert*-butyl acid, there is an increase in bonding for the C−H bond going from anti to gauche relative to the *tert*-butyl group. Meanwhile, the other C−H bond shows a decrease in bond order that is less than that of the silyl case. A similar pattern is seen in the bond lengths and charges on the hydrogens, with the silyl acid showing a greater lengthening of bonds and increase in charge on the hydrogens.

As might be expected, results suggesting quite compact conformations were obtained in calculations performed on both anions in the gas phase. The silyl-carboxylate gauche conformer is predicted to have a close (2.7 Å) interaction between carboxylate oxygen and silicon, which requires that the distribution of methyl groups around the silicon be distorted[17] to accommodate the interaction. With the *t*-butyl anion, the corresponding distance is larger (3.8 Å) between the carboxylate oxygen and carbon. For both trimethylsilyl and *tert*-butyl substituents, the calculations suggest that the gauche conformations are predicted to be more stable than the anti. Overstabilization of compact conformers is a known limitation on gas-phase calculations of charged species.[18]

SCHEME 2. (a) Anti and (b) Gauche Inductively Destabilized Conformers of 3-(Trimethylsilyl)propionate



2a **2b**

The observed decrease in stabilization of the silyl anionic anti conformer, which is not observed for the *tert*-butyl anion in more weakly polar solvents, may result from an unusual expression of the *β*-silyl effect depicted in Scheme 2. When the carboxylate and silicon are gauche, the silicon is anti to one of the hydrogens that is α to the carbonyl. Thus, that C−H bond is well-aligned to receive electron density from the silicon **2b**, as computationally predicted above from bond lengthening and charge changes. This electron donation to the hydrogen, hyperconjugatively stabilizes the carboxylic acid. Simultaneously, the silicon−hydrogen hyperconjugation inductively destabilizes the carboxylate, to which it is cross-conjugated. Meanwhile, in the anti conformation, **2a** orbital overlap between the C−Si and C−H bonds in question is decreased as both methylene hydrogens α to the carbonyl make 60° dihedral angles to the C−Si bond. The balance of stabilization and destabilization predicted by gas-phase computation does not tell us what happens in solvents, but to the extent the results are meaningful, it is reasonable that the effect vary with solvent polarity, because the charge separation associated with the hyperconjugation effect will be moderated in solvents of high dielectric constant.[19] On the other hand, if the negative carboxylate oxygen is calculated in the gas phase to be close enough to interact with silicon electrostatically or otherwise, this effect would be expected to be moderated by solvent dielectric constant in the opposite way, more gauche in less polar solvents and less gauche in more polar solvents.

Conclusions

In summary, evidence from ^1H NMR spectroscopy indicates that 3-(trimethylsilyl)propionic acid and its anion have a strong preference for anti in both protic and aprotic solvents, believed to arise from steric hindrance modulated by an inductive destabilization associated with hyperconjugative gauche interaction between the trimethylsilyl and carboxyl substituents. Corresponding trends were absent in *tert*-butylpropionic acid.

Experimental Section

Synthesis of Ethyltrimethylsilane.[20]Ethyl Grignard was prepared in 20 mL of dry tetrahydrofuran from 1.75 g (72 mmol) of magnesium granules and 5.5 mL (8.03 g, 73.6 mmol) of ethyl

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[14] Compared to the ±5% accuracy of the anti percentages.

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[17] The C−Si−C bond angle into which the oxygen interleaves is distorted to 113°; the other $CH_3-Si-CH_3$ angles are 104°.

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[20] (a) This compound has been prepared via a reaction between ethyl Grignard and trimethylsilyl sulfate (Sommer, L. H.; Kerr, G. T.; Whitmore, F. C. *J. Am. Chem. Soc.* **1948**, *70*, 445−447) as well as reaction between methyl Grignard and ethyltrichlorosilane. (b) Bygdén, A., Ph.D. Dissertation, Uppsala University, 1916. (c) Whitmore, F. C.; Sommer, L. H.; Di Giorgio, P. A.; Strong, W. A.; Van Strien, R. E.; Bailey, D. L.; Hall, H. K.; Pietrusza, E. W.; Kerr, G. T. *J. Am. Chem. Soc.* **1946**, *68*, 475−481. (d) Although its ^{29}Si and ^{13}C spectra have been reported before (Schraml, J.; Chvalovsky, V.; Magi, M.; Lippmaa, E. *Col. Czech. Chem. Com.* **1979**, *44*, 854−865), a search of the literature failed to yield a proton spectrum.

bromide. Once addition was complete, the mixture was allowed to stir until cool. With intermittent cooling via ice-bath, a solution of 6.3 mL (5.43 g, 50 mmol) of trimethylsilyl chloride in 20 mL of tetrahydrofuran was added dropwise to the Grignard solution. After addition was complete, the mixture was allowed to warm to room temperature and then heated to reflux for 1 h. After being cooled again to room temperature, the mixture was transferred to a separatory funnel. Solids in the reaction flask were dissolved in ice−water and transferred to the separatory funnel. After removal of the aqueous layer, the organic phase was extracted five times with 40 mL of cold water to remove the THF and any polar byproducts. The remaining organic layer was dried over sodium sulfate. The resulting ethyltrimethylsilane (3.5 g, 69%) possessed a sweetish, oily odor reminiscent of alkenes. The proton NMR spectrum (300 MHz, $CDCl_3$) gave peaks at 0.933 (t, $J = 7.9$ Hz, 3.00 H), 0.474 (q, $J = 7.9$ Hz, 1.91 H), and −0.022 ppm (br s, 9.05 H). The ^{13}C NMR spectrum (75 MHz, $CDCl_3$) gave peaks at 8.573 (s), 7.556 (s), and −1.982 ppm (s).

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Supporting Information Available: Characterization data (^1H and ^{13}C NMR spectra) for ethyltrimethylsilane and computational data (Cartesian coordinates, tables) for TSPA and its anion and 4,4-dimethylpentanoic acid and its anion in the gas phase. This material is available free of charge via the Internet at http://pubs.acs.org.

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