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Conformations of *N*,*N*-diethyl-β-alanine and β-alanine as a function of solvent

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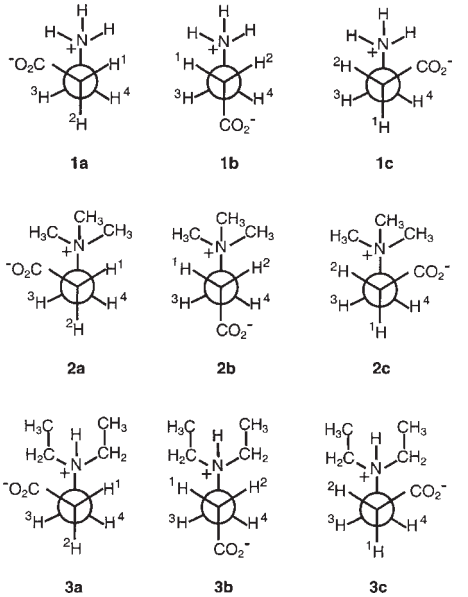
ABSTRACT: Conformational equilibria of *N*,*N*-diethyl-β-alanine were estimated from vicinal proton–proton coupling constants between the —CH_2—CH_2— group in protic and aprotic solvents of different polarities. β-Alanine was similarly studied in dimethyl sulfoxide (DMSO). In general, the results for both substances correspond fairly well with those reported earlier for β-alanine in neutral and acidic aqueous solutions. There appeared to be little conformational preference for *N*,*N*-diethyl-β-alanine in any of the solvents used, ranging from water to dichloromethane. The exception was a moderate preference (66–73%) for the *trans* conformer displayed by the conjugate base of *N*,*N*-diethyl-β-alanine in all of the solvents studied. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: *N*,*N*-diethyl-β-alanine; β-alanine; conformation; solvent

INTRODUCTION

In research reported earlier, it was found that β-alanine (**1a–c** as the dipolar ion) and many of its derivatives and analogs showed little preference beyond the statistical proportions in water solution for the *gauche* or the *trans* conformation, whether as conjugate acids, dipolar ions or conjugate bases as measured by NMR vicinal couplings.[1] Even such compounds as *N*,*N*,*N*-trimethyl-β-alanine **2** (as the dipolar ion) appear to exist fairly close to statistical conformational equilibrium, despite the fact that *N*,*N*,*N*-trimethylammonium group might be regarded as a relatively large group with respect to steric hindrance.[1] Indeed, 1-(*N*,*N*,*N*-trimethylammonium)-3,3-dimethylbutane is regarded as being essentially the standard for favorableness of *trans* conformations.[2] This behavior of **2** was rationalized by recalling that the rotational barrier of nitromethane is much lower than that of ethane [0.8 kcal mol^{-1} (1 kcal = 4.184 kJ)[3,4]], most likely because, in nitromethane, there is a threefold CH_3 substituent rotating opposite to a twofold NO_2 substituent, corresponding to the substitution pattern for **2**.[1] Although the situation for **2** does not involve rotation about directly attached substituents, one can expect generally that bringing a planar carboxylic acid group up edgewise to a tetrahedral trimethylammonium group will not be as likely to have the same direct eclipsed interactions at close distances as would be the case for two staggered tetrahedral groups.

A further point with β-alanine is that the change in the conformational equilibrium was found to be small both with temperature and with solvent dielectric constant.[1]



A serious problem with **1** is that it has low solubility in non-polar solvents and we have been unable to extend the measurements of the conformational equilibria of this substance to less polar solvents than methanol or dimethyl sulfoxide and, in the latter solvent, concentrations of only about 0.004 M could be attained at ambient temperatures. Scouting experiments showed that *N*,*N*-

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diethyl-β-alanine (**3a–c** as the dipolar ion) had little conformational preference in water and, because this substance is soluble in many non-polar solvents, we have surveyed its conformational preferences in several less polar, protic and non-protic solvents.

EXPERIMENTAL

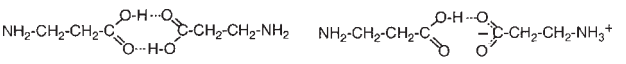
N,*N*-Diethyl-β-alanine was purchased as the hydrochloride and converted to the neutral dipolar form by shaking an aqueous solution with a suspension of Amberlite IRA-440C and then removing the water under reduced pressure. β-Alanine was commercial material and used without further purification.

The ^{1}H NMR spectra were taken of $\sim$0.05 M solutions of 3 and $\sim$0.04 M solutions of **1** with 300 and 500 MHz spectrometers at ambient temperature. Many of the 300 MHz spectra of **3** had overlapping lines and 500 MHz spectra were required to measure or confirm the shifts and couplings obtained, or that were unattainable, at 300 MHz. In many solvents, the hydrogen on nitrogen of the dipolar form of **3** did not often give a recognizable signal, because of (1) rapid intermolecular proton exchange, (2) proton–deuterium exchange with the solvent, (3) rapid quadrupolar relaxation induced by ^{14}N or (4) complex splitting of the proton resonance with the three adjacent CH_2 groups. The presence of this proton on nitrogen, when exchange was slow (whether deuteriated or not), was easily visible by display of diastereotopic shifts and splittings of the *N*,*N*-diethyl methylene protons but not, of course, those of the β-methylene group of **3**.

Spectra of **3** were taken at the ambient acidity generated when the substance was dissolved in the various solvents. Solutions of the conjugate acids of **3** were obtained by adding excess trifluroacetic acid, and the conjugate bases were generated by adding a 2 : 1 excess of tetrabutylammonium cyanide,[5] except in water where excess NaOD or DCl was added to solutions of **3** in D_2O.

DISCUSSION

Spectra of the very dilute solutions of neutral **1** in DMSO displayed some unexpected complexations, there being two sets of —CH_2—CH_2— protons with different chemical shifts and with different intensities. Each set was a pair of triplets and the relative intensities were variable, but appeared to depend on the concentrations of **1** and adventitious water. Addition of small amounts of water caused the smaller set of triplets to diminish in intensity and it is assumed that the larger triplets are those of uncomplexed **1**. Because DMSO is not a good solvent for anions, we believe that the unassigned peaks may arise from some variety of dimer complex such as **4** or **5**. For **5**, it probably would be necessary for proton exchange to occur between the amino groups to have equivalent pairs of methylene groups.[6] In any case, all of the observed triplets were typical A_2B_2 patterns.



4 **5**

When trifluoroacetic acid was added to the very dilute solutions of **1** in DMSO, the resonances of the CH_2 attached to nitrogen were split into six lines, as expected for additional couplings with a directly attached, non-exchanging ammonium group. Surprisingly, in one case, the smaller triplets we ascribed above to dimer formation did not disappear on adding acid. When tetrabutylammonium cyanide was added as a base to dipolar **1** in DMSO, there was exchange broadening of the lines arising from the CH_2 attached to nitrogen and disappearance of the smaller triplet and substantial changes in chemical shifts. The data for **1** in DMSO are summarized in Table 1.

The chemical shifts and couplings between the vicinal α- and β-methylene protons and those of the *N*-ethyl groups of **3** were extracted from the observed spectra, when necessary, with the aid of a True BASIC version of LCN3 written by Bothner-By and Castellano,[7] and are listed in Tables 2–4. Many of the spectra of the vicinal

Table 1. Chemical shifts and $^3J_{HH}$ couplings for β-alanine in DMSO

	N—CH_2— protons		—CH_2—CO_2 protons		
Solution	Shift (ppm)	$^3J_{HH}$ coupling (Hz)	Shift (ppm)	$^3J_{HH}$ coupling (Hz)	Fraction[a]
Acidic, (lg)[b,c]	2.97	6.3 ± 0.3[d]	2.57	6.9 ± 0.4	5 : 1
(sm)[e]	3.14	6.5 ± 0.5[f]	2.64	6.8 ± 0.3[f]	
Neutral (lg)[c]	2.87	6.0 ± 0.1	2.30	6.3 ± 0.4	2–3 : 1
(sm)[e]	2.83	$\sim$6.0	2.15	6.3 ± 0.3	
Basic (lg)[c,g]	2.5[h]	—[h]	1.83	6.3 ± 0.4	—

[a] Strong : weak triplets as measured by integrations.
[b] Trifluoroacetic acid was the added acid.
[c] Shifts and couplings of larger triplets.
[d] Sextet.
[e] Shifts and couplings of smaller triplets.
[f] Broad peaks.
[g] Tetrabutylammonium cyanide added.
[h] Broad resonance with no fine structure; no smaller triplets.

Table 2. Chemical shifts (ppm) and $^3J_{HH}$ couplings (Hz) for neutral *N*,*N*-diethyl-β-alanine in various solvents

Solvent	δCH_3 (Et)	δCH_2 (Et)	$^3J_{HH}$ (Et)	$\delta^a_{H3,H4}$	$\delta^b_{H1,H2}$	$^3J^c_{H1,2H3,4}$
D_2O	1.30	3.23	7.31	3.34	2.61	7.01
CD_3OD	1.32	3.21	7.32	3.28	2.53	6.59
CD_3CD_2OD	1.31	3.21	7.23	3.26	2.50	6.59
$(CD_3)_3COD$	1.31	3.13	7.28	3.18	2.50	6.47
DMSO-d_6	1.01	2.65	7.18	2.77	2.28	6.78
CD_3CN	1.13	2.82	7.18	2.89	2.35	6.41
$CD_3(CO)CD_3$	1.11	2.75	7.18	2.85	2.40	6.47
CD_2Cl_2	1.18	2.82	7.25	2.88	2.43	6.46
$CDCl_3$	1.23	2.91	7.31	2.98	2.52	6.39
THF-d_8	1.02	2.56	7.14	2.72	2.33	6.94

[a] Protons of NCH_2—.
[b] Protons of —CH_2CO_2.
[c] The protons on C1 were equally coupled to those of C2, which corresponds to 66% *gauche*.

Table 3. Chemical shifts (ppm) and $^3J_{HH}$ couplings (Hz) for *N*,*N*-diethyl-β-alanine in various solvents with added trifluoracetic acid

Solvent	δCH_3 (Et)	δCH_2 (Et)	$^3J_{HH}$ (Et)	$\delta^a_{H3,H4}$	$\delta^b_{H1,H2}$	$^3J^c_{H1,2H3,4}$
D_2O	1.33	3.27	7.31	3.45	2.91	6.96
CD_3OD	1.33	3.27	7.31	3.42	2.81	6.87
CD_3CD_2OD	1.33	3.25	7.31	3.42	2.82	7.07
DMSO-d_6	1.20	3.15	7.32	3.28[d]	2.73	7.33
CD_3CN	1.26	3.18[d]	7.33	3.32[d]	2.77	6.72
$CD_3(CO)CD_3$	1.45	3.54[d]	7.32	3.66	3.02	6.78
CD_2Cl_2	1.37	3.27[e]	7.33	3.40	2.93	6.23
THF-d_8	1.31	3.25	7.25	3.40	2.83	7.35

[a] Protons of NCH_2—.
[b] Protons of —CH_2CO_2.
[c] The protons on C1 were equally coupled to those of C2, which corresponds to 66% *gauche*.
[d] Broad line, ± 0.01 ppm.
[e] Broad line, ± 0.03 ppm.

α- and β-methylene protons were simple triplets with J_{13} equal to J_{14}, with only small variations in coupling constants. To calculate the positions of the conformational equilibria, we assumed that the rotational angle θ between the *N*,*N*-diethylamino (or ammonium) group and carboxyl (or carboxylate) group is 60° for the *gauche* conformer and 180° for the *trans* conformer. The validity of this assumption is questionable, but at present we have nothing much better to go on.[8,9] On the basis of this assumption, we use the procedures of Haasnoot *et al.*[10] and Altona and co-workers[11,12] to estimate the appropriate H–H coupling constants of the respective 60° *gauche* and 180° *trans* conformers. The estimated equilibrium proportions so calculated of the conformers are also listed in Table 1. We should mentions, at least parenthetically, that equal vicinal coupling constants of

Table 4. Chemical shifts (ppm) and $^3J_{HH}$ couplings (Hz) for *N*,*N*-diethyl-β-alanine in various solvents with excess added base

Solvent	δCH_3 (Et)	δCH_2 (Et)	$^3J_{HH}$ (Et)	$\delta^a_{H3,H4}$	$\delta^b_{H1,H2}$	$^3J_{13}$	$^3J_{14}$	%T[c]
D_2O	0.82	2.32	7.23	2.55	2.13	5.52	10.59	68
CD_3OD	1.09	2.63	7.23	2.88	2.35	5.51	10.56	68
$(CD_3)_3COD$	1.17	2.50	7.16	2.82	2.24	5.28	11.01	73
DMSO-d_6	0.92	2.39	7.12	2.54	1.94	5.55	10.15	66
THF-d_8	—[d]	—[d]	7.12	—[d]	—[d]	5.35	10.76	71

[a] Protons of NCH_2—.
[b] Protons of —CH_2CO_2.
[c] Percentage of *trans* conformer.
[d] Not referenced.

about 7 Hz, which are assumed here to arise from $\theta = 60°$ *gauche* and 180° *trans* in 2/3 to 1/3 respective proportions, could also be the result of having one conformer with θ being about 45° as a possibility for the dianion of 1,4-butanedioate in THF.[5] However, while in the case of the dianion, this possibility is supported by quantum calculations, that is not true of corresponding calculations for **1**.[1]

Even a cursory inspection of the data for **3** in Table 2 reveals much that is unexpected on the basis of what we might call conventional wisdom. For example, in the conformational distributions of the dianion of 1,4-butanedioic acid, in an ROH series ranging from water to *tert*-butyl alcohol, the proportion of *trans* increased steadily, just as would be expected for increasingly strong electrostatic repulsions between the negative carboxylate charges as the dielectric constant decreased from 78 to 11.[13] However, when the solvent was changed to be aprotic dimethyl sulfoxide (DMSO) or tetrahydrofuran (THF), very substantial amounts of the *gauche* dianion conformer were present.[5,13]

One might expect that something akin to these changes might, or should, take place with **3** as a function of solvent polarity through electrostatic interactions, but there is a major difference in that **3** is overall neutral and the requirements for solvation by the solvents should be much less rigid than for a dianion. Another factor is the state of ionization of **3** in aprotic solvents. The fact is that, in less polar solvents, ammonium ions become better proton donors and carboxylate ions become stronger bases, so that there is a strong tendency for the dipolar forms of β-amino acids to be converted to the non-polar forms. This can be seen in the proton chemical shifts of the methylene groups connected to the nitrogen and the carboxylate group. Those protons closest to nitrogen move upfield $\sim$0.6 ppm for the change from D_2O to THF, while the α-methylene protons move upfield by $\sim$0.3 ppm. Interestingly, in $CDCl_3$, surely expected to be a better hydrogen-bonding solvent than THF, the shift changes are smaller. We conclude, therefore, that **3** exists, in the aprotic solvents we have used, as the non-polar form unless extra acid is added. The shift trends of **3** in *tert*-butyl alcohol suggest that, even though this solvent is protic, a substantial fraction of the non-polar form could be present.

For **1** and many of its analogs or substitution products in water, the conformational preferences are small, which suggests that electrostatic, hydrogen bonding and steric effects are all unimportant, unless these effects operate in opposite directions to average to produce essentially null resultants. With **3** as its conjugate base, irrespective of the solvent being protic, aprotic, polar or non-polar, the situation is different, in that now *trans* is favored, there being 27–32% of the *gauche* form present. Why is that? This question is especially relevant when we see that in acidic solutions in the same solvents, the conjugate acid shows no obvious conformational preferences.

When we look at the spectra of the conjugate acid of **3** in the solvents in which it has been studied, we know that the nitrogen is protonated, because there are extra splittings of the β-methylene protons, the α-methylene protons of the ethyl groups are now diastereotopic and more splittings are observed than expected for that structural feature alone, which arises from the presence of the proton on nitrogen. The latter feature disappeared slowly with acetone-d_6 as solvent because the trifluoroacetic acid present caused H–D exchange with the solvent so that the nitrogen proton became deuteriated.

We are still left with the question as to why the conjugate acid of **3** shows little conformational preference but the corresponding conjugate base has substantially different preferences. One possibility is steric hindrance involving the ethyl groups of the conjugate base of **3**, even though **2**, with *N*-methyl groups, does not show the same effects. The late Frank C. Whitmore had an adage that 'ethyl groups can flap more asymmetrically than methyl groups' and that seems likely to be the situation here. But is a protonated *N*,*N*-diethylammonium group likely to have less of a steric effect than an unprotonated *N*,*N*-diethylamino group? Our conjecture at this point is that the protonated group will be conformationally more rigid than the unprotonated group, which can undergo rapid inversion at its unprotonated nitrogen. The more rigid protonated diethylammonium group might be able to find steric accommodation with a carboxyl group more easily than a floppy, rapidly inverting, unprotonated *N*,*N*-diethylamino group.

It appears for **3** that one can rationalize the observed conformational preferences as a function of solvent and protonation, even though the reasoning required to do this may not be very obvious from an initial encounter with the data sets in Tables 2–4.

Acknowledgments

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