Conformations of 2-Carboxy-1,4-butanedioic Acid as a Function of Ionization State in Dimethyl Sulfoxide
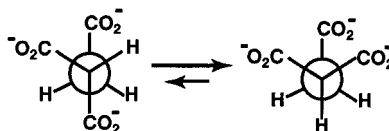
Gautham Nair and John D. Roberts*

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

robertsj@caltech.edu

ABSTRACT

The conformational equilibria of 2-carboxy-1,4-butanedioic acid and its mono-, di-, and trianions were estimated by NMR couplings in dimethyl sulfoxide (DMSO). Intramolecular hydrogen bonding was inferred for the mono- and dianions, but not for the triacid. For the di- and trianions, the $^3J_{HH}$ couplings were consistent with the negative carboxylate groups being much closer together than might be expected from electrostatic repulsion considerations. The successive triacid pK_a values were estimated as 7.0, 13.4, and ~20(?) on the Bordwell scale.

In extending our studies of conformational equilibria and acid−base behavior of dicarboxylic acids as a function of solvent,[1−5] we have investigated the analogous behavior of 2-carboxy-1,4-butanedioic acid **1** and its deprotonated forms. The particular points of interest were the degree and mode of intramolecular hydrogen-bond formation, the influence of the charges in the several ionized species on the relative proportions of the possible conformations, and the ionization constants of the triacid in DMSO. Because **1** allows for both a 1,3-propanedioic-type interaction and a 1,4-butanedioic-type interaction, competition between these two modes of intramolecular hydrogen bonding, steric effects, and Coulombic repulsion (especially in the trianion) are expected to play important roles in fixing conformational preferences.

All evidence indicates that the three main conformers (**1a**, **1b**, and **2**) of 2-carboxy-1,4-butanedioic acid can be assumed to be very rapidly interconverted on the NMR time scale by rotation about the central C−C bond. Of these conformers, **1a** and **1b** are enantiomers, while **2** has a plane of symmetry. This conformational system thus parallels that offered by the usual 1,2-disubstituted ethanes in that the "gauche−trans" forms **1a** and **1b** would be expected to amount to 2/3 of its mixture with the "gauche−gauche" form **2** if the position of the conformational equilibrium were purely statistical. Determination of the position of conformational equilibrium was achieved by analysis of the average vicinal proton−proton coupling constant, *J*. This coupling can be related to the fraction of each conformer present in the mixture by comparing it to estimates of coupling constants for pure conformers. Of the several procedures for such estimations, we use the one developed by Altona and co-workers,[6−8] which employs empirical group electronegativities (λ) as-

(1) Lit, E. S.; Mallon, F. K.; Tsai, H. Y.; Roberts, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 9563−9567.

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

(3) Kent, D. R., IV; 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*, 4481−4486.

(4) Choi, P. J.; Petterson, K. A.; Roberts, J. D. *J. Phys. Org. Chem.* **2002**, *15*, 278−286.
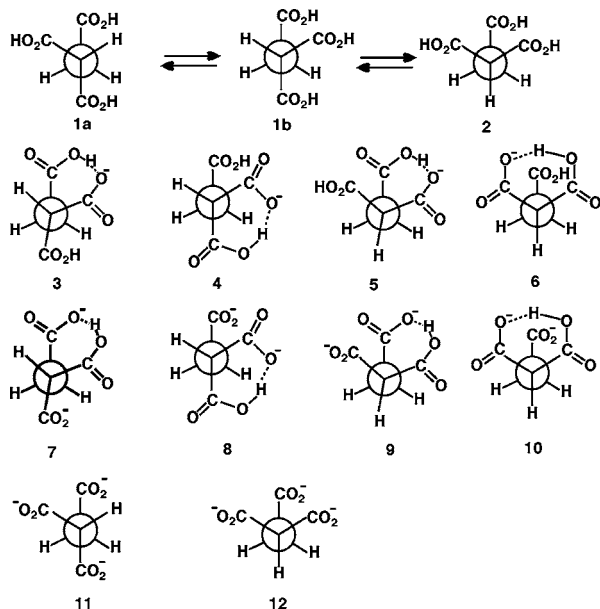
(5) Cheng, J. M.; Heller, J. P.; Petterson, K. A.; Roberts, J. D. *Magn. Reson. Chem.* **2002**, *40*, 666−671.

(6) Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792.

(7) Altona, C.; Ippel, J. H.; Westra Hoekzema, A. J. A.; Erkelens, C.; Groesbeek, M.; Donders, L. A. *Magn. Reson. Chem.* **1989**, *27*, 564−567.

sociated with each substituent as parameters in a Karplus relationship between J and the dihedral angle.

The average vicinal proton–proton coupling constants could be read directly from the NMR spectra, given the simplicity of the AX_2 system. Measurement of the triacid coupling constant was straightforward. The average estimated vicinal proton–proton coupling constant J_{est} is expected to have a different value for a mix of conformers **1a** and **1b** than for **2**, because with **1a** and **1b**, J_{est} will be the average of a small gauche and a large trans coupling, while with **2**, J_{est} will be the average of two gauche-type couplings. In general, values of vicinal proton–proton coupling constants depend weakly on the nature of the substituents but more strongly on the dihedral angle between them. If we are to use J_{obs} to estimate the composition of the mixture of conformers, we need to be able to provide estimates of the respective coupling constants of each conformation. Experimental values of dihedral angles in solution are not well established, so the usual procedure is to simply assume the 60–180° convention between the substituents. However, there are indications from quantum calculations[3] and experiment[9,10] that this may bring with it significant error, even for trans conformations, where steric effects should be minimal. Because we have no evidence to the contrary, we will, for now, assume the 60–180° convention for the triacid, recognizing the uncertainty generated by our assumption. Then, with the aid of Altona's estimated values for COOH,[8] one obtains $J_{12} = 3.4$ Hz and $J_{13} = 13.6$ Hz for **1a**, averaging to a $J_{est} = 8.5$ Hz for **1a** and **1b**, and $J_{12} = J_{13} = J_{est} = 3.7$ Hz for the gauche couplings in **2**. The NMR spectra at room temperature of the triacid in DMSO show a sharp doublet with $J_{obs} = 7.4$ Hz for the methine proton. Using the 8.5

(8) Altona, C.; Francke, R.; de Haan, R.; Ippel, J. H.; Daalmans, G. J.; Westra Hoekzema, A. J. A.; van Wijk, J. *Magn. Reson. Chem.* **1994**, *32*, 679–678.
(9) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456–463.
(10) Price, D. J.; Roberts, J. D.; Jorgenson, W. L. *J. Am. Chem. Soc.* **1998**, *120*, 9672–9679.

and 3.7 Hz values expected for pure **1** and **2**, respectively, the equation $7.44 = 8.5 \times F1 + 3.7(1 - F1)$ is obtained, giving an estimate of the mole fraction of **1**, $F1 = 0.76$. This is not far from the statistical value of 0.667. That there is no strong preference for a particular conformation suggests that intramolecular hydrogen-bond formation in DMSO for the triacid is probably not significant, a conclusion consistent with findings for 1,4-butanedioic acid.[1,2,10]

The ionization constants of acids in DMSO (Bordwell[9] scale) can be determined by observing the changes in chemical shift that occur when a test acid of known pK_a in DMSO is added to a solution of the conjugate base of the compound being studied.[4] The pK_a for the first ionization of acid **1** in DMSO, 7.0, is much closer to the 7.2 value for 1,3-propanedioic acid than to the 9.5 for 1,4-butanedioic acid. Thus, the first ionization of the triacid in DMSO should be at one of the geminal carboxylic groups. For practical purposes, we assume that the only possibilities are structures **3**, **4**, **5**, or **6** (or mixtures thereof along with the corresponding enantiomers and isomers of **4** that differ in which of two oxygens is the hydrogen-bond acceptor).

The −0.63 ppm chemical-shift change of the methine proton and only a −0.01 ppm corresponding shift of the methylene protons resulting from the first ionization provide substantial confirmation of ionization of one of the geminal carboxyl groups. That structures **3**–**6** are all shown with hydrogen bonding is consistent with findings for propanedioic and 1,4-butanedioic acids in DMSO.[3,4] However, to be comparable with those findings,[3] the dihedral angles of **3** and **5** should be increased to 70°, as needed to allow for formation of a favorable hydrogen bond,[1,10] and supported by studies of the conformation equilibria of 1,4-butanedioic acid in THF and alcohols.[2,3]

The NMR spectra of the methylene protons of the monoanion showed a sharp doublet with $J_{obs} = 4.9$ Hz. This suggests that any diastereotopic chemical shifts of protons 1 and 2, as well as J_{12} and J_{13}, are averaged over the two monoanion structures corresponding to **1a** and **1b**. To interpret J_{obs}, the estimated couplings for the hydrogen-bonded **3** and **5** must be calculated under the assumption of a 70° dihedral angle, not the idealized 60°.[2,3] The Altona estimates of J_{est}, the average of J_{12} and J_{13} for **3** and **5**, change from 8.62 and 3.40 Hz in the 60° case to 7.72 and 3.59 Hz, respectively, for the 70° structures. If we assume that only either **3** or **4** and either **5** or **6** exist in the mixture, calculated percentages of $3/(3 + 5) = 31\%$, $3/(3 + 6) = 35\%$, $4/(4 + 5) = 26\%$, and $4/(4 + 6) = 29\%$ are obtained. This gives us some idea of the range to be expected for the various combinations of conformers. It is clear that there is more **5** and/or **6** (the average is 70%) than **3** and/or **4** (on average 30%). This could be the result of some extra hydrogen-bonding interaction of the un-ionized carboxyl, but we have no concrete evidence for that.

Whether the hydrogen-bonding pattern of **3** or **4** is the more favorable is quite a puzzle. When the first ionization of a dibasic acid in DMSO results in a hydrogen-bonded anion, there will be interplay between the intrinsic strength of the acid, the strength of the hydrogen bond, and the

Table 1. Summary of Spectra and Conformational Preference of 2-Carboxy-1,4-butanedioic Acid

species	CH$_2$ shift, ppm	CH shift, ppm	pK_a	J_{obs}, Hz	% of conformers[a]
triacid	2.68	3.54	7.0	7.4	24 **2**/(**1** + **2**)
monoanion	2.67	2.91	13.4	4.9 ± 0.1	71 ± 2 **6**/(**4** + **6**)
dianion	2.26	2.80	~20 ?	4.8 ± 0.1	76 ± 2 **10**/(**8** + **10**)
trianion	2.0	2.9	—	6.1 ± 0.2	51 ± 4[b] **12**/(**11** + **12**)

[a] Calculated on the basis of 60°/180° dihedral angles in the conformers. Reported uncertainties do not reflect possible uncertainties in Altona's estimation procedure or the choice of dihedral angle. The second line refers to the structures in the article: the given percentage is the fraction of the species in the numerator in a mixture of the two species in the denominator. The equilibrium expected on a purely statistical basis is 33%. [b] Most likely a lower bound. Could increase to 68% using another reasonable set of dihedral angles. See text.

solvation energy of the anion. The second ionization reflects the Bjerrum−Kirkwood−Westheimer[11−13] electrostatic energy required to remove a second acid proton from the more-or-less distant carboxylate charge, along with the hydrogen-bond strength and the solvation energy of the dianion. The pK_2 − pK_1 value for propanedioic acid in DMSO is 11.4, while that of 1,4-butanedioic acid, also in DMSO, is 7.2.[4] This could be regarded as indicating that the hydrogen bond of **4** is stronger than that of **3**, but one cannot be completely sure because contributions from electrostatic effects and solvation energy differences between acid and base are also entangled into pK_2 − pK_1. Since **4**-type bonding is the best candidate, the values reported in Table 1 use the 60−180° convention and reflect only the experimental uncertainty associated with the measurement of J_{obs}.

The second ionization of the triacid produces a −0.41 ppm shift change of the methylene protons and only a −0.11 change of the methine proton and is evidence that the second ionization is of the 4-carboxyl group. The similarity between the pK_2 − pK_1 value of 6.4 for acid **1** and 7.2 for butanedioic acid, as opposed to the 11.4 value for propanedioic acid, corroborates this claim. Structures **7**−**10** show some possible conformers of the dianion. Structures **7** and **9** are assumed to have 70° dihedral angles.

The average coupling constant for the dianion, J_{obs}, is 4.8 Hz and is only slightly different from that of the monoanion (4.9 Hz). Like the monoanion, the dianion also shows a substantial preference for the gauche−gauche structures (**9** and/or **10**) over gauche−trans (**7** and/or **8**). Averaging over the four possible combinations, as in the monoanion case, indicates that there is 74% **9** or **10** and 26% **7** or **8** in the mixture. Formation of either **9** or **10** should result in increased electronic repulsion, but the high observed mole fraction indicates that it might be compensated for by formation of a bifurcated hydrogen bond in **10**, involving all three carboxyl groups. However, the observed confor-

mational preference might also reflect the apparent tendency to adopt conformations in which carboxylate groups in aprotic solvents stay closer to one another than might otherwise be expected.[3] The third ionization was difficult to achieve, but it is clear that this ionization caused the conformational equilibrium to move closer to the gauche−trans form (**11**). The J_{obs} of 6.1 Hz observed in several preparations suggests that **11** and its enantiomer are still less favored than **12** when compared to a purely statistical 66%: 33% equilibrium, provided that we assume the 60−180° dihedral angle convention. This quite unexpected bunching of three negative carboxylate groups has a close parallel in the substantial amounts of the gauche conformer estimated for the dianion of 1,4-butanedioic acid in tetrahydrofuran.[3]

The waters become murkier because theoretical calculations suggest that the dihedral angle between vicinal carboxylates in aprotic solvents could be as small as 40°.[3] If this were the case for the trianion, we could assume that the carboxylates of **11** and **12** equilibrate between the two structures with 40° dihedrals. Using the Altona relations to estimate J_{12} and J_{13} values and then assuming a 40° dihedral in **11** only, in **12** only, or in both **11** and **12**, we obtained respective **11**/(**11** + **12**) percentages of 40, 41, and 32%. Thus, it appears that the ~1:1 ratio of **11**/**12** estimated by assuming the 60−180° dihedral convention is an approximate upper bound to the actual conformational equilibrium.

Supporting Information Available: Procedures for determination of the pKa values. This material is available free of charge via the Internet at http://pubs.acs.org.

OL030089O

(11) Bjerrum, N. *Z. Physik. Chem.* **1923**, *106*, 219−242
(12) Kirkwood, J. G.; Westheimer, F. H. *J. Chem. Phys.* **1938**, *6*, 506−512.
(13) Westheimer, F. H.; Kirkwood, J. G. *J. Chem. Phys.* **1938**, *6*, 512−517.