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Asymmetry of the “Strongest” OHO Hydrogen Bond, in the Monoanion of (±)-α,α′-Di-*tert*-butylsuccinate

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Abstract: The large pK_a difference between first and second deprotonations of (±)-α,α′-di-*tert*-butylsuccinic acid has been interpreted as evidence for a short, strong intramolecular hydrogen bond in the monoanion. Incorporation of ^{18}O into one carboxyl group allows investigation of the symmetry of the H-bond in solution by the method of isotopic perturbation. Relative to the intrinsic ^{18}O-induced isotope shift at the carboxyl carbon, as measured in the diacid, an additional isotope shift of 8 ppb in methanol, 14 ppb in acetone, and 5 ppb in THF is observed for potassium hydrogen (±)-α,α′-di-*tert*-butylsuccinate-^{18}O. This increase indicates that the ion exists as an equilibrating pair of interconverting tautomers and not as a single symmetric resonance hybrid. The X-ray crystal structures of the tetrapropylammonium, tetrabutylammonium, tetrabutylphosphonium, magnesium, and calcium hydrogen (±)-α,α′-di-*tert*-butylsuccinate salts show a remarkably short O−O distance of 2.41 Å, consistent with a strong hydrogen bond. However, the dicesium salt of the (±)-α,α′-di-*tert*-butylsuccinate dianion also shows the short O−O distance of 2.41 Å, so this cannot be taken as evidence for a strong hydrogen bond in the monoanion. Moreover, the two O−H distances in the monoanions are unequal, and the hydrogen bond is asymmetric in these crystals. It is concluded that there is no evidence for any special stabilization associated with symmetric H-bonds. The large ΔpK_a difference is therefore not due to any feature of the H-bond itself but is attributed to the electrostatic repulsion between the carboxylates in the dianion, which is relieved in the monoanion by inserting a proton between the carboxylates.

Introduction

Hydrogen bonding (H-bonding) is a stabilizing interaction between a proton donor, A−H, and a proton acceptor, B. If the basicities of A and B are equal or nearly so, the H-bonded complex most commonly involves a pair of rapidly interconverting tautomers, A−H···B and A···H−B.[1] The energy governing the H motion in such an H-bond is a double-well potential. However, as the A−B distance decreases, the barrier to H motion is lowered below the zero-point energy of the vibration. The energy governing the H motion has become a single-well potential, and there is only a single symmetric species, A−H−B. For the case of oxygens as donor and acceptor, this change occurs as the O−O distance approaches 2.4 Å and the O−H and H···O distances both approach 1.2 Å.[2] In particular, the formate−formic acid complex is calculated to reach maximum H-bond strength at an O−O distance of 2.4 to 2.5 Å (depending on computational level), and the barrier to H motion is less than the zero-point energy.[3] Likewise, the H-bond in 3-hydroxypropenal becomes symmetric at 2.24 Å,[4] presumably shorter because the OHO path is curved. Indeed, neutron-diffraction studies show that the H-bond in the enol of nitromalonamide is asymmetric.[5]

An alternative approach to inducing a single-well potential lies in the transition from $AH{\cdot}B$ to $A^-{\cdot}HB^+$.[6] In the complex between chloroacetic acid and pyridine the proton is on O at higher temperature but moves to N at low temperature, where the zwitterion is favored by the increased polarity due to more highly ordered solvent dipoles. At an intermediate temperature the ^{1}H chemical shift reaches a maximum, which is consistent with a quasisymmetric $A^{\delta-}\cdots H\cdots B^{\delta+}$.

Yet such symmetric H-bonds are unusual.[7] Concomitant with the decrease of the A−B distance, the strength of the H-bond increases, so that they can have up to 38.6 kcal/mol of stabilization energy, as in FHF^-.[8] They may be referred to as short or strong or low-barrier H-bonds, depending on the criterion used to distinguish them. The unusual strength of symmetric H-bonds is often attributed to the resonance stabilization associated with two identical resonance forms (e.g., **1a** ↔ **1b**). Depending on the framework, such H-bonds have been classified as charge-assisted or resonance-assisted H-bonds, or

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[1] Hibbert, F.; Emsley, J. *Adv. Phys. Org. Chem.* **1990**, *26*, 255–379. Jeffrey, G. A. *An Introduction to Hydrogen Bonding*; Oxford, 1997.

[2] Peinel, G. *Chem. Phys. Lett.* **1979**, *65*, 324–326.

[3] Smallwood, C. J.; McAllister, M. A. *J. Am. Chem. Soc.* **1997**, *119*, 11277–11281.

[4] Woodford, J. N. *J. Phys. Chem. A* **2007**, *111*, 8519–8530.

[5] Madsen, G. K. H.; Wilson, C.; Nymand, T. M.; McIntyre, G. J.; Larsen, F. K. *J. Phys. Chem. A* **1999**, *103*, 8684–8690.

[6] Golubev, N. S.; Denisov, G. S.; Smirnov, S. N.; Shchepkin, D. N.; Limbach, H. H. *Z. Phys. Chem.* **1996**, *196*, 73–84. Smirnov, S. N.; Golubev, N. S.; Denisov, G. S.; Benedict, H.; Schah-Mohammedi, P.; Limbach, H. H. *J. Am. Chem. Soc.* **1996**, *118*, 4094–4101. Shenderovich, I. G.; Burtsev, A. P.; Denisov, G. S.; Golubev, N. S.; Limbach, H. H. *Magn. Reson. Chem.* **2001**, *39*, S91–S99.

[7] Perrin, C. L. *Pure Appl. Chem.* **2009**, *81*, 571–583. Lau, J. S.; Perrin, C. L In *Isotope Effects in Chemistry and Biology*; Kohen, A.; Limbach, H. H., Eds.; CRC Press: Cleveland, OH, 2005; Chapter 8.

[8] Larson, J. W.; McMahon, T. B. *Inorg. Chem.* **1984**, *23*, 2029–2033.

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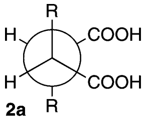
as H-bonds with covalent character.[9] That greater strength is presumed to compensate for the 15−20 kcal/mol required to expand the O−H distance from the normal 1.0 Å to 1.2 Å, as inferred from O−H stretching frequencies. Furthermore, because of the strength of these H-bonds, they have been proposed to stabilize intermediates and transition states in some enzyme-catalyzed reactions,[10] although this is a matter of some controversy.[11]

$$\underset{\mathbf{1a}}{\mathrm{F{-}H\ F^-}} \leftrightarrow \underset{\mathbf{1b}}{\mathrm{F^-\ H{-}F}}$$

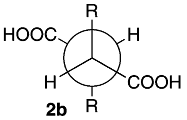
According to diffraction studies, most conclusively neutron diffraction, several monoanions of dicarboxylic acids are symmetric in the crystal, with their H centered between two oxygens.[12,13] We have been seeking such symmetric H-bonds in solution. Nevertheless, all dicarboxylate monoanions so far have been found to be a mixture of tautomers, rather than a single, symmetric structure.[14] The contrast between crystals and solution has been attributed to the disorder of the local environment, which instantaneously solvates one of the carboxyls better than the other. This disorder may be imposed by H-bonding to the carboxylate by a protic solvent or by a closer association of the cation with the carboxylate in an aprotic organic solvent. This disorder in the solvation environment has been modeled for potassium hydrogen phthalate.[15]

We therefore turn to the most likely candidate, the dicarboxylate monoanion with the "strongest" H-bond between the carboxylic acid and carboxylate groups. The criterion we choose as a gauge of H-bond strength is ΔpK_a, the difference between the first and second acid-dissociation constants, pK_{a1} and pK_{a2}.[16] The stabilization of the monoanion by intramolecular H-bonding acidifies the diacid and lowers pK_{a1}. Moreover, that stabilization decreases the acidity of the H within the H-bond and increases pK_{a2}. There is a further contribution to ΔpK_a from the electrostatic repulsion of the two carboxylates in the dianion, which increases pK_{a2} but does not affect pK_{a1}. However, an alternative criterion using double the difference between pK_{a1} and pK_E, the pK_a of the corresponding monoester, gives nearly the same relative values.[10b]

For maleic acid ΔpK_a is 4.65, and for phthalic acid it is only 2.30,[17] the latter not so far above the $\log_{10} 4$ from statistics. Therefore the evidence that these have strong H-bonds in water is tenuous, although in DMSO, where H-bonding becomes more important, ΔpK_a increases to 15.6 or 11.0.[18] In contrast, α,α′-dialkylsuccinic acids with bulky alkyl groups show large ΔpK_a values in aqueous ethanol, but only for the racemic stereoisomers, denoted with (±).[19] The large ΔpK_a was associated with the steric bulk of the alkyl groups, which favor a conformation (**2a**) that places the carboxyl groups in proximity and allows formation of a strong intramolecular H-bond in the monoanion. In contrast, in the meso stereoisomer the favored conformation (**2b**) keeps not only the alkyl groups but also the carboxyl groups apart. The largest ΔpK_a, 9.54, is for (±)-α,α′-di-*tert*-butylsuccinic acid (**2a**, R = $C(CH_3)_3$). Alternatively, $2(pK_{a1} - pK_E)$ for this acid is 7.72, which is also unusually large. Moreover, the enthalpy of the second ionization is 4.8 ± 0.8 kcal/mol more positive (more endothermic) than estimated for the non-H-bonded anion; this difference represents an estimate of the enthalpy of formation of the H-bond, separate from electrostatics.[20] This is thus the diacid whose monoanion is most likely to exhibit an exceptionally strong H-bond. In solution it is stronger even than that of FHF^-, whose 38.6 kcal/mol is a gas-phase strength but whose ΔG and ΔH for formation in water from HF + F^- are only −0.54 and +1.5 kcal/mol (endothermic!), respectively.[21] We now probe the symmetry of the H-bond in (±)-α,α′-di-*tert*-butylsuccinate monoanion by NMR studies in solution and by X-ray crystallography.



2a



2b

The method of isotopic perturbation of equilibrium has been used to investigate the symmetry of the H-bonds in the monoanions of 1,2-dicarboxylic acids.[14,22] It depends on the measurement of the isotope shift (isotope effect on ^{13}C NMR chemical shift), $^n\Delta$, due to an isotope *n* atoms distant from the reporter nucleus (eq 1).[23] Because heavy isotopes generally lead to an upfield shift, $^n\Delta$ is usually negative. Two contributions to the observed isotope shift can be distinguished, namely an intrinsic shift, Δ_o, owing simply to the presence of an isotope, and a shift, Δ_{eq}, induced by the perturbation of an equilibrium (eq 2).

$$^n\Delta = \delta_{\text{heavy}} - \delta_{\text{light}} \tag{1}$$

$$\Delta_{\text{obs}} = \Delta_o + \Delta_{\text{eq}} \tag{2}$$

To understand Δ_{eq} for the monoanion of a dicarboxylic acid, we must consider how mono-^{18}O substitution can perturb a hypothetical equilibrium between tautomers (**3a** and **3b**, plus an additional tautomer **3b′** that is protonated on the ^{16}O of the ^{18}O-labeled carboxyl and whose presence merely halves the

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(9) Gilli, P.; Bertolasi, V.; Ferretti, V.; Gilli, G. *J. Am. Chem. Soc.* **1994**, *116*, 909–915. Gilli, P.; Bertolasi, Pretto, L.; Ferretti, V.; Gilli, G. *J. Am. Chem. Soc.* **2004**, *126*, 3845–3855.

(10) (a) Gerlt, J. A.; Kreevoy, M. M.; Cleland, W. W.; Frey, P. A. *Chem. Biol.* **1997**, *4*, 259–267. (b) Frey, P. A.; Cleland, W. W. *Bioorg. Chem.* **1998**, *26*, 175–192. (c) Cleland, W. W. *Arch. Biochem. Biophys.* **2000**, *382*, 1–5.

(11) Guthrie, J. P *Chem. Biol.* **1996**, *3*, 163–170. Perrin, C. L.; Nielson, J. B. *Annu. Rev. Phys. Chem.* **1997**, *48*, 511–544. Schutz, C. N.; Warshel, A. *Proteins: Struct., Funct., Bioinf.* **2004**, *55*, 711–723. Olsson, M. H. M.; Parson, W. W.; Warshel, A. *Chem. Rev.* **2006**, *106*, 1737–1756.

(12) (a) Darlow, S. F.; Cochran, W. *Acta Crystallogr.* **1961**, *14*, 1250–1257. (b) Darlow, S. F. *Acta Crystallogr.* **1961**, *14*, 1257–1259.

(13) (a) Tomkinson, J.; Braid, I. J.; Howard, J.; Waddington, T. C. *Chem. Phys.* **1982**, *64*, 151–157. (b) Howard, J.; Tomkinson, J.; Eckert, J.; Goldstone, J. A.; Taylor, A. D. *J. Chem. Phys.* **1983**, *78*, 3150–3155. (c) Fillaux, F.; Leygue, N.; Tomkinson, J.; Cousson, A.; Paulus, W. *Chem. Phys.* **1999**, *244*, 387–403.

(14) (a) Perrin, C. L.; Thoburn, J. D. *J. Am. Chem. Soc.* **1989**, *111*, 8010–8012. (b) Perrin, C. L.; Thoburn, J. D. *J. Am. Chem. Soc.* **1992**, *114*, 8559–8565. (c) Perrin, C. L. *Science* **1994**, *266*, 1665–1668. (d) Perrin, C. L.; Nielson, J. B. *J. Am. Chem. Soc.* **1997**, *119*, 12734–12741. (e) Perrin, C. L.; Lau, J. S. *J. Am. Chem. Soc.* **2006**, *128*, 11820–11824.

(15) Garcia-Viloca, M.; González-Lafont, À.; Lluch, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 9198–9207.

(16) (a) McCoy, L. L.; Nachtigall, G. W. *J. Am. Chem. Soc.* **1963**, *85*, 1321–1324. (b) McCoy, L. L. *J. Am. Chem. Soc.* **1967**, *89*, 1673–1677.

(17) Jencks, W. P.; Regenstein, J. *Handbook of Biochemistry*, 2nd ed.; Chemical Rubber Co.: Cleveland, OH, 1970.

(18) Choi, P. J.; Petterson, K. A.; Roberts, J. D. *J. Phys. Org. Chem.* **2002**, *15*, 278–286.

(19) Eberson, L. *Acta Chem. Scand.* **1959**, *13*, 211–223.

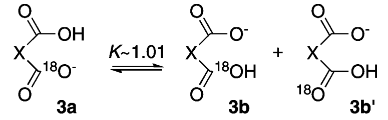
(20) Eberson, L.; Wadsö, I. *Acta Chem. Scand.* **1963**, *17*, 1552–62.

(21) Salomon, M.; Stevenson, B. K. *J. Chem. Eng. Data* **1974**, *19*, 42–4.

(22) Perrin, C. L.; Nielson, J. B.; Kim, Y. J. *Ber. Bunsen. Phys. Chem.* **1998**, *102*, 403–409.

(23) Hansen, P. E. *J. Labelled Compd. Radiopharm.* **2007**, *50*, 967–981.

overall isotope effect). Owing to vibrational frequencies and zero-point energies, an ^{18}O-labeled carboxylic acid is ~1% less acidic than an ordinary carboxylic acid.[24] Consequently, the tautomeric equilibrium is shifted slightly toward **3b** and **3b′**, with an equilibrium constant $K = ([\mathbf{3b}] + [\mathbf{3b'}])/[\mathbf{3a}] \approx 1.01$. Moreover, the ^{13}C NMR chemical shift of a carboxyl group, δ_{COOH}, is different from that of a carboxylate, $\delta_{\mathrm{CO_2^-}}$. These chemical shifts can be estimated as 176 and 180 ppm, respectively, from independent measurements on the diacid and the dianion (or less reliably, from the diacid and the monoanion). Of course, owing to rapid interconversion, separate signals for carboxylic acid and carboxylate groups are not seen in the monoanion, but only an average. That average is a weighted average, perturbed by the equilibrium. It is readily shown that the perturbation shift, Δ_{eq}, is given by eq 3.[25] According to the values estimated, the carbon attached to ^{18}O is thus shifted upfield by ~0.02 ppm, relative to the carbon attached to ^{16}O. This is in addition to an upfield Δ_o of 0.026 ppm per ^{18}O, which can be measured independently in the ^{18}O-labeled diacid (or dianion). The signature of a tautomeric mixture is thus an additional isotope shift in the monoanion, greater than that in the diacid or dianion, and this was indeed seen in succinic acid (**3**, X = CH_2CH_2).

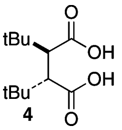


$$\Delta_{\mathrm{eq}} = \frac{K-1}{K+1}(\delta_{\mathrm{COOH}} - \delta_{\mathrm{CO_2^-}}) \qquad (3)$$

We now report that the monoanion of (±)-α,α′-di-*tert*-butylsuccinic acid shows an isotope shift greater than the intrinsic isotope shift. This is evidence that this anion exists in solution as an equilibrating pair of tautomers, not as a single symmetric species. Indeed, the X-ray crystal structures of five salts of the monoanion show asymmetric H-bonds. Moreover, the diacid and dianion are found to have very similar crystal structures.

Results

Synthesis. (±)-α,α′-Di-*tert*-butylsuccinic acid (**4**) and anhydride were readily obtained by the literature procedure.[26] Incorporation of one ^{18}O was facile, by hydrolysis of the anhydride in $Na^{18}OH-H_2{}^{18}O$. Incorporation of a single ^{18}O was confirmed by mass spectroscopy. The labeled or unlabeled monoanion (**5** or **5**-^{18}O) was generated by treating the diacid with 1 equiv of potassium acetate. Potassium hydrogen α,α′-di-*tert*-butylsuccinate was then isolated by concentrating the solution to dryness and washing with ether to remove acetic acid. It is soluble in methanol, acetone, and THF.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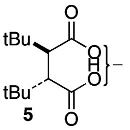
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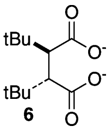
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Table 1. Chemical Shifts (ppm) and Isotope Shifts (ppb) for Mono-^{18}O-labeled (±)-α,α′-Di-*tert*-butylsuccinic Acid (**4**) and Its Monoanion (**5**)

solvent	δ, **4**	δ, **5**	$-\Delta_o$, **4**	$-\Delta_{\mathrm{obs}}$, **5**	$-\Delta_{\mathrm{eq}}$
$CDCl_3$			23		
CD_3OD	176.75	180.02	24	32	8
acetone-d_6	175.2	177.93	22	36	14
THF-d_8	182.88	183.95	25	30	5
D_2O			29[a]		

[a] Dianion **6**.

(±)-α,α′-Di-*tert*-butylsuccinate dianion (**6**) and hydrogen monoanion (**5**) were crystallized with various counterions, as well as the diacid (**4**). The anhydride was hydrolyzed under basic conditions and converted to the diacid. Quaternary ammonium and phosphonium salts were prepared by dissolving the diacid or the anhydride in an aqueous solution containing 1 equiv of the quaternary hydroxide and concentrating the solution under vacuum to give an oily residue. Suitable crystals of the tetrapropylammonium, tetrabutylammonium, tetrabutylphosphonium, magnesium, and calcium salts of the monoanion were obtained, as well as the cesium salt of the dianion. The diacid could be crystallized from aqueous acetone. To supplement X-ray data on the diacid, its structure was also modeled with the MM2 force field.

Isotope Shifts. Incorporation of one ^{18}O results in an isotope shift (eq 1), Δ, which can be measured as the difference between the ^{13}C NMR chemical shifts of the unlabeled and ^{18}O-labeled carboxyl groups. It is always upfield and therefore has a negative value. Figure S1 shows the carboxyl region of the ^{13}C NMR spectra of mono-^{18}O-labeled (±)-α,α′-di-*tert*-butylsuccinic acid and the potassium salt of its monoanion in three solvents. The intrinsic isotope shift, Δ_o, was obtained from the diacid **4** (or the dianion, which is soluble only in D_2O). Values are presented in Table 1. The average, −25 ± 3 ppb, is consistent with previous intrinsic isotope shifts due to a single ^{18}O.[27] Values of Δ_{obs} are also presented in Table 1. The key result is that the magnitude of Δ_{obs}, obtained from potassium hydrogen (±)-α,α′-di-*tert*-butylsuccinate-^{18}O in three different solvents, is significantly greater than Δ_o.

Therefore there is an equilibrium isotope shift, Δ_{eq}, equal to the difference between Δ_{obs} and Δ_o and included in Table 1. The value varies with solvent, but the variation may not be significant. If the variation of isotope shift with solvent is real, it is probably due to variations of δ_{COOH} and $\delta_{\mathrm{CO_2^-}}$, which enter into eq 3.

Crystal Structures. Crystallographic data for α,α′-di-*tert*-butylsuccinic acid and six of its salts are summarized in Table S1. The crystal structures confirm a racemic mixture. For example, the unit cell of the tetrapropylammonium salt contains four molecules of each enantiomer, eight tetrapropylammonium ions, and four molecules of water H-bonded to carbonyl oxygens but not in proximity to the H-bonded oxygens. Other salts contain two symmetry-independent ion pairs, but the calcium salt shows two symmetry-equivalent monoanions. The structure of a hydrogen (*R*,*R*)-α,α′-di-*tert*-butylsuccinate anion within a crystal of tetrapropylammonium hydrogen (±)-α,α′-di-*tert*-butylsuccinate is shown in Figure 1.

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(24) Ellison, S. L. R.; Robinson, M. J. T. *J. Chem. Soc., Chem. Commun.* **1983**, 745–746. Tanaka, N.; Araki, M. *J. Am. Chem. Soc.* **1985**, *107*, 7780–7781.

(25) Siehl, H.-U. *Adv. Phys. Org. Chem.* **1987**, *23*, 63–163.

(26) Eberson, L. *Acta Chem. Scand.* **1959**, *13*, 40–49.

(27) Risley, J. M.; Van Etten, R. L. *NMR* **1990**, *22*, 81–168.

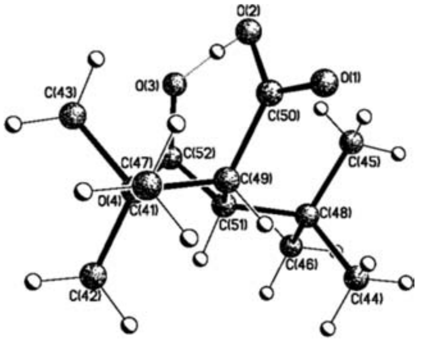

Figure 1. Crystal structure of hydrogen (*R*,*R*)-α,α′-di-*tert*-butylsuccinate viewed along central C(49)−C(51) bond.

Table 2 lists selected distances and angles from the seven structures. Negative dihedral angles are reported as positive.

Discussion

Comments on Synthesis. Steric repulsion of *tert*-butyl groups complicates the synthesis of α,α′-di-*tert*-butylsuccinic acid. Its diethyl ester is accessible by dimerization of the $(CH_3)_3CCHCOOC_2H_5$ radical, produced by oxidative decarboxylation of the monoethyl ester of *tert*-butylmalonic acid. A 6:5 mixture of meso and racemic stereoisomers was obtained. The ratio was measured by ^{1}H NMR integration, and the assignment was based on the assumption that the downfield *tert*-butyl signal is the racemic diester, as in the case of the diacids.

The 6:5 ratio of diethyl esters shows that steric repulsions do not control diastereoselectivity in the radical dimerization. This is a general result with radical couplings,[28] although there are exceptions.[29] The low stereoselectivity here is probably because the radical−radical coupling is so exothermic that the radical faces need only encounter each other, while the *tert*-butyls rotate apart and avoid each other.

Incorporation of a single ^{18}O label into α,α′-di-*tert*-butylsuccinic acid was achieved by hydrolysis of its anhydride with $Na^{18}OH$ in $H_2{}^{18}O$, followed by acidification. Conversion of the racemic diacid into the anhydride occurs readily (which is what permits the separation of the racemic anhydride from the meso diacid). Consequently careful handling is necessary to prevent the dehydration of the labeled diacid and further equilibration of the carboxyl oxygens with the $H_2{}^{18}O$, which would result in a statistical mixture of multiply labeled diacid isotopologues. Nevertheless, the observation of two ^{13}C NMR signals of comparable intensity indicates monoincorporation. Moreover, mass spectrometric analysis indicated that the isolated diacid was 85.7% mono-^{18}O-labeled and 14.3% unlabeled. This level of isotopic incorporation is lower than the 97% of the $H_2{}^{18}O$ and is most likely due to introduction of trace $H_2{}^{16}O$ along with the hygroscopic powdered NaH during the preparation of $Na^{18}OH$. It is important that the proportion of unlabeled diacid be low, or else its ^{13}C NMR signal would appear between the two signals of the mono-^{18}O-labeled material and diminish the resolution.

Isotope Shifts and H-Bond Symmetry in Solution. According to the data in Table 1, the observed isotope shifts Δ_{obs} of potassium hydrogen α,α′-di-*tert*-butylsuccinate in three different organic solvents are greater (in magnitude) than the intrinsic isotope shift Δ_o that is observed in the diacid. As with other dicarboxylate monoanions,[14] this increase is attributable to the perturbation of an equilibrium by the isotopic label and indicates that the H-bonded monoanion exists as a pair of tautomeric structures.

The firm conclusion is that the monoanion is not a single, symmetric structure. Moreover, the variations of isotope shift with solvent should not be taken as evidence for any variations in symmetry. Indeed, the question of symmetry must be answered either Yes or No, and here the answer is No. The variations of isotope shift are then probably due to variations of δ_{COOH} and $\delta_{CO_2^-}$, which enter into eq 3 but are not independently measurable except in diacid or dianion, which are imperfect models.

We again attribute the asymmetry to interactions with the local environment.[14,15] The disorder of solvation, whether by H-bonding by protic solvent or by electrostatic interaction with the countercation or by orientation of the solvent dipoles, renders the two carboxylate groups instantaneously unequal. The proton then attaches to the less well solvated carboxylate.

H-Bond Distances and H-Bond Symmetry in Crystals. According to the X-ray data, the O−O distance in α,α′-di-*tert*-butylsuccinic diacid (**4**) is 2.54 Å. Even though the diacid contains an OHO H-bond between one COOH and the other C=O (whose OH is exo), it is not a short H-bond. In contrast, the salts of its hydrogen monoanion (**5**) exhibit an O−O distance across the H-bonded oxygens of between 2.41 and 2.45 Å (2.466 Å in the calcium salt, where one oxygen is coordinated to the metal ion). This is comparable to the shortest H-bonds in various salts of the monoanion of maleic acid, which range from 2.39 to 2.46 Å. So short an O−O distance would suggest the formation of a very strong H-bond.

However, the same short distance, 2.415 Å, is seen in the cesium salt of the dianion, which of course cannot have a stabilizing H-bond. Instead, those adjacent oxygens, with partial negative charges, repel. Some of the electrostatic repulsion due to this short distance is unquestionably relieved by coordination of both oxygens of each carboxylate to the cesium cation. Of course, this relief is not as effective as that obtained by inserting a hydrogen directly between two oxygens. Nevertheless, the short O−O distance, even in the dianion, suggests that this is an inescapable feature of the conformation of many α,α′-di-*tert*-butylsuccinate anions. It cannot be used as evidence for a very strong H-bond in the monoanion.

More definitive is the observation that the H in all five salts is closer to one of the oxygens than to the other and that the two O−H distances in monoanion **5** are definitely unequal. Therefore this does not have a symmetric H-bond, in agreement with the isotopic perturbation results from NMR spectroscopy in solution. The asymmetry in solution has been attributed to an intrinsic asymmetry due to the disorder of the solvation environment.[14,15] The asymmetry in the crystals may be due to a static asymmetry of the placement of the counterion, or to crystal packing forces. Indeed, the alkyl groups of the tetraalkylammonium or tetraalkylphosphonium counterion are wrapped so that the two oxygens are not in the same environment, and the distances from the N^+ or the P^+ to the two exo (C=O) oxygens of the carboxylate are slightly different. The $Ca(OH_2)_4{}^{+2}$ is located even more asymmetrically, in that it is coordinated to only one oxygen of each of the two dicarboxylate monoanions. However, the $Mg(OH_2)_6{}^{+2}$ is placed symmetrically with respect to the monoanions, with equal distances between a water of hydration and the O=C−OH and the O=C−O···H

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(28) Matsumura, Y.; Nishimura, M.; Watanabe, M.; Kise, N; Aoyama, Y.; Kashimura, S. *Electrochim. Acta* **1997**, *42*, 2233–2239.

(29) Klotz-Berendes, B.; Schäfer, H. J.; Grehl, M.; Fröhlich, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 189–191.

Table 2. Selected Bond Lengths (*d*, Å), Bond Angles (ϕ, deg), and Torsional Angles (τ, deg) in Hydrogen (±)-α,α′-Di-*tert*-Butylsuccinate Anion (**5**), (±)-α,α′-Di-*tert*-butylsuccinate Dianion (**6**), and (±)-α,α′-Di-*tert*-butylsuccinic Acid (**4**)

	Pr_4N^+**5**	Bu_4N^+**5**	Bu_4P^+**5**	$Mg_{1/2}^+$**5**	$Ca_{1/2}^+$**5**	Cs^+_2**6**	**4**	**4**[a]
d_{O-O}	2.416	2.411	2.406	2.45[b]	2.462	2.415	2.56	
d_{O-H}	1.06	1.03	1.01	0.85[b]	1.06		1.14	
$d_{O-H'}$	1.36	1.42	1.41	1.61[b]	1.41		1.48	
$d_{C=O}$[b]	1.228	1.224	—[c]	1.235	1.231	1.235[d]	1.20	1.208
d_{C-OH}[b]	1.281	1.290	—[c]	1.284	1.299	1.290[e]	1.30	1.345
$d_{Me_3CC-CCMe_3}$	1.524	1.517	—[c]	1.566[b]	1.558	1.556[b]	1.531	1.557
d_{Me_3C-C}[b]	1.589	1.598	1.60	1.579	1.584	1.578	1.591	1.564
d_{C-CO}[b]	1.529	1.544	1.528	1.537	1.522	1.531	1.584	1.525
ϕ_{O-H-O}	166	159	166	170	170	—	155	
$\phi_{Me_3C-C-CCMe_3}$[b]	114.1	113.9	—[c]	115.4	115.7	115.2	115.8	117.8
$\phi_{O_2C-C-CCO_2}$[b]	116.2	115.6	116	114.6	115.5	115.4	110	115.0
$\phi_{Me_3C-C-CO_2}$[b]	111.5	112.2	114 ± 9[c]	112.2	110.3	111.4	118	112.2
$\tau_{Me_3C-C-C-CMe_3}$	166.7	167.9	167.4	168.8[b]	168.7	167.3[b]	170.7	167.5
$\tau_{O_2C-C-C-CO_2}$	70.5	72.5	68.4	73.6[b]	72.4	71.3[b]	84	79.9
$\tau_{Me_3C-C-C-CO_2}$[b]	61.4	59.8	62 ± 6	58.8	59.9	60.7	52.6	56
$\tau_{O=C-C-CCO_2}$[b]	133	132.5	135	131.3	133	131.3[d]		
$\tau_{O-C-C-CCO_2}$[b]	49	49.5	49	51.7	48.6		50.4	
$\tau_{H-O-C-O}$[b]	166	167 ± 17		171	176.6		166[b]	
$\tau_{H-O-C-C}$[b]	17	16 ± 16		13	5.8			

[a] MM2. [b] Average. [c] Disordered. [d] Exo. [e] Endo.

oxygens. Nevertheless, even in this salt, where the environment appears to be symmetric, the H-bond of the monoanion is asymmetric. Therefore there is no symmetric H-bond that might be stabilized by symmetry *per se*.

Other Distances. The C−O distances in all five hydrogen α,α′-di-*tert*-butylsuccinates are consistent with a monoanion with an intramolecular H-bond. Each carboxyl group exhibits two distinct C−O bond distances, a 1.29 Å distance to the oxygen involved with the intramolecular H-bond and a 1.22 Å distance to the oxygen that is not. For comparison, the average bond distances in the diacid are 1.345 Å to the hydroxyl oxygen and 1.21 Å to the carbonyl oxygen, whereas a typical carboxylate possesses two 1.254 Å C−O distances.[30] Therefore the C−O distances in the H-bonded monoanion are slightly equalized, as in a carboxylate, but remain close to those in a carboxylic acid. It should be noted that the two C−O distances in each carboxylate group of the dianion are different, presumably owing to different O−Cs distances.

The central $C_\alpha-C_\alpha'$ bond distance in **5** is a very ordinary 1.55 Å, not distorted by any steric repulsions. The distance between the α and *tert*-butyl carbons is 1.58 Å, which is slightly longer than the typical 1.556 Å distance between a quaternary and tertiary carbon and closer to the 1.588 Å between two quaternary carbons.[30] The longer distance is consistent with the geometry of another 1,2-di-*tert*-butyl species.[31]

Bond Angles and Dihedral Angles. Although bond lengths are constrained not to vary widely, bond angles and dihedral angles are more flexible and may be more informative about the short O−O distance in **5**. According to the data in Table 2, the average OHO angle for five monoanions is 166°. This is very close to the average of 163° that is seen in a wide variety of crystals and that is consistent with the 180° that is considered to be optimum for H-bonding.[32]

If the H-bond in the dianion is not a short, strong one, can the bond angles and dihedral angles account for the large ΔpK for (±)-α,α′-di-*tert*-butylsuccinic acid? The data in Table 2 do not show any unusual bond angles in the monoanion. The average C−C−C angle between the *tert*-butyl, α, and α′ carbons is 115°; the average angle between the carboxyl, α, and α′ carbons is 115.6°; and the average angle between the *tert*-butyl carbon and the geminal carboxyl carbon is 112°. All these values are close to the average C−C−*t*Bu angle of 113.7° in a similar 1,2-di-*tert*-butyl species.[31] They contrast markedly with the opening of the $C=C-CO_2$ angle to 130° in the maleate monoanion.[33]

The $Me_3C-C-C-CO_2$ dihedral angles in **5** are maintained very close to the 60° of an ideal gauche conformation. Therefore the interaction between a *tert*-butyl and a vicinal carboxyl involves minimal steric repulsion and entails no distortion. This is consistent with the conformational analysis of 4,4-dimethylpentanoic acid, which tolerates 30% gauche.[34]

Small distortions are seen in the other dihedral angles around the central C−C bond of monoanion **5**. Distortion is not possible with maleate and phthalate monoanions, where the sp^2 carbons constrain the $O_2C-C-C-CO_2$ fragment to be coplanar, with a 0° dihedral angle. That rigidity leaves opening of the $C=C-CO_2$ angle as the only means to adjust the O_2C-CO_2 distance. In contrast, the sp^3 carbons of **5** permit an $O_2C-C-C-CO_2$ dihedral angle of 71.5°, wider than the 60° of an ideal gauche conformation. The carboxyls have twisted apart to accommodate the H-bond. This is consistent with 71° calculated as optimal for an intramolecular H-bond,[35] with 70° derived from three-bond $^1H-^1H$ NMR couplings,[36] and with 80° in the gas phase and 74°−75° in aqueous solution, according to DFT calculations and Monte Carlo simulations.[37]

Furthermore, to accommodate the opening of the dihedral angle between the carboxyls in **5**, the *tert*-butyls are pushed

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(30) Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. *J. Chem. Soc., Perkin Trans. 2* **1987**, S1–S19.

(31) Bragg, S.; Johnson, J. E. B.; Graziano, G. M.; Balaich, G. J.; Heimer, N. E. *Acta Crystallogr.* **2002**, *E58*, o1010–o1012.

(32) Taylor, R.; Kennard, O. *Acc. Chem. Res.* **1984**, *17*, 320–326.

(33) Hsu, B.; Schlemper, E. O. *Acta Crystallogr.* **1980**, *B36*, 3017–3023.

(34) Nkansah, R. A.; Gerken, J. B.; Roberts, J. D. *J. Org. Chem.* **2007**, *72*, 6956–6960.

(35) Lit, E. S.; Mallon, F. K.; Tsai, H. Y.; Roberts, J. D. *J. Am. Chem. Soc.* **1993**, *115*, 9563–9567. Williams, L. N.; Petterson, K. A.; Roberts, J. D. *J. Phys. Chem. A* **2002**, *106*, 7491–7493.

(36) Kent, D. R., IV; Petterson, K. A.; Gregoire, F.; Snyder-Frey, E.; Hanley, L. J.; Muller, R. P.; Goddard, W. A., III; Roberts, J. D. *J. Am. Chem. Soc.* **2002**, *124*, 4481–4486.

(37) Price, D. J.; Roberts, J. D.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1998**, *120*, 9672–9679.

toward each other, so that the average dihedral angle between them is 168°, rather than the 180° of an ideal anti conformation. Nevertheless, the *tert*-butyls remain sufficiently far apart that they do not repel each other. Also there is no repulsion between *tert*-butyl and carboxyl, as documented above. The key result is that rotation around the $C_\alpha C_\alpha'$ axis increases the distance between the carboxyl groups. Without that increase, the O−O distance of the intramolecular H-bond would be too short, less than the 2.41 Å that seems to be optimum.

Finally, the carboxyls twist by an average of 50° about the C—C bond, maintaining the $O_2C—CO_2$ distance but bringing two oxygens into proximity and permitting the H-bond. The HOCO and HOCC dihedral angles are rotated by no more than 10°−15° from planarity. The H is anti (to the C═O), which is the less favorable conformation of a carboxyl group,[38] but this is what is required for the H-bond. This feature does not reduce the H-bond strength, because the donor lone pair is also anti, so that the basicities of the H acceptor and the conjugate base of the H donor remain identical, as required.

Nevertheless, comparison of the data in Table 2 shows that dianion **6** has almost the same bond angles and dihedral angles as those of monoanion **5**, and diacid **4** is not much different. The key feature is the proximity of the carboxyls to each other, in all three species. Because proximity enforces repulsion between the carboxylates in the dianion, proximity itself cannot then be responsible for strengthening the H-bond in the monoanion.

Symmetry, Strain, H-Bond Strength, and Resonance Stabilization. There is no question that as the O−O distance decreases, the barrier to H motion must eventually decrease below the zero-point energy, so that a double-well potential becomes effectively a single-well one. An example of this transformation is ice compressed at ≥110 GPascal, whereupon it becomes ice X.[39] Further examples where steric crowding reduces O−O distances and appears to strengthen H-bonds are in *o*-hydroxy acylaromatics and the enol of 2-pivaloyl-1,3-indandione.[40]

Both a large ΔpK_a and a short O−O distance are associated with strong H-bonds. However, the compilation in Table S2 and the graph of those data in Figure S2 deny a correlation between ΔpK_a and O−O distance in dicarboxylate monoanions. For example, chloromaleate and maleate exhibit nearly the same 2.40-Å O−O distance, but the ΔpK_a values are 2.14 and 4.65, respectively. (Chloromaleate has a centered H, despite an apparent imbalance of basicities of the two donor oxygens, and the imbalance would only increase ΔpK_a, not decrease it.) Besides, the “best” linear correlation has the O−O distance increasing with ΔpK_a, not decreasing.

Does steric strain compress the O−O distance? The presence of *tert*-butyl groups would seem to be an obvious guarantee of steric strain. However, the *tert*-butyls are anti and well separated from each other. We judge that steric strain is of little consequence for α,α′-di-*tert*-butylsuccinic acid derivatives. The strain arises instead because the carboxyls are forced into proximity, compressing the O−O distance. This strain is present not only in monoanion **5** but also in diacid **4** and dianion **6**. Indeed, there is little variation in structure across this series, and the O−O distance is nearly the same in **6** as in **5**.

Yet this compression cannot strengthen the H-bond in **5**, but must weaken it. If the compression were relaxed, **5** would become more stable. Therefore unusual stability should not be ascribed to a symmetric or low-barrier H-bond. Indeed, both the NMR evidence and the X-ray crystal structure of **5** indicate that it is not symmetric.

The asymmetry of **5** raises the question of the role of resonance in stabilizing H-bonds. The unusual strength of symmetric H-bonds is often attributed to the resonance stabilization that is maximized with two identical resonance forms, as in **1a** ↔ **1b**. However, the asymmetry of the H-bond in **5** means that the two resonance forms are not identical, and its H-bond does not benefit from a maximum resonance stabilization. Moreover, that asymmetry means that the stabilization associated with two identical resonance forms is not so great as to constrain the H-bond to be symmetric. Even enols of *β*-dicarbonyl compounds, which are unquestionably resonance-stabilized, do not have symmetric H-bonds. Their resonance involves their pi systems, whereas the H-bond is sigma. Therefore resonance does not influence their H-bonds, despite their designation as resonance-assisted H-bonds.[9]

Why then are H-bonds found to be symmetric in some crystals? Inasmuch as resonance seems to be incapable of compensating for the energy cost of expanding the OH distance from 1.0 to 1.2 Å, we must fall back on crystal-packing forces as responsible for symmetrizing the H-bond.

We must acknowledge that the potential surface in this monoanion does not necessarily correspond to a double well. All that these results require is that there be a mixture of tautomers, rather than a single symmetric species. An alternative is a single-well potential, but where the instantaneous solvation stabilizes an asymmetric structure. As the solvation changes, the hydrogen moves across the H-bond, and there may be a multitude of possible hydrogen positions. Such dynamic structures have been distinguished as solvatomers, signifying isomers (here tautomers) that differ in solvation,[14e] and the equilibrium between them can be perturbed by isotopic substitution.

In summary, we conclude that there is no special stabilization associated with symmetric H-bonds. If there were extra stabilization associated with symmetry, symmetric H-bonds ought to be more common and more readily detectable.

Origin of Large ΔpK_a. A popular criterion of H-bond strength in dicarboxylate monoanions is ΔpK_a. Thus (±)-α,α′-di-*tert*-butylsuccinic acid, with the largest ΔpK_a, 9.54, is considered to have the “strongest” H-bond of any dicarboxylate monoanion. However, its H-bond is not symmetric, and there is no resonance stabilization associated with symmetry to account for the strength of the H-bond.

Thus the large ΔpK_a cannot be attributed to the formation of a symmetric H-bond in **5**. Is the ΔpK_a large because the H-bond is strong, albeit asymmetric? We reject this possibility, because there is no independent evidence for a strong H-bond in solution in the absence of the resonance stabilization associated with symmetry.

Is the large ΔpK_a due to some sort of strain? Above we judged that steric strain arising from the *tert*-butyl groups is of little consequence for α,α′-di-*tert*-butylsuccinic acid derivatives. There is strain in monoanion **5** because the carboxyls are forced into proximity, compressing the O−O distance, but the O−O distance is nearly the same in **6** as in **5**. The difference between

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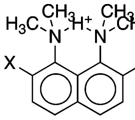
(38) Wiberg, K. B.; Laidig, K. E. *J. Am. Chem. Soc.* **1987**, *109*, 5935–5943.

(39) Sugimura, E.; Iitaka, T.; Hirose, K.; Kawamura, K.; Sata, N.; Ohishi, Y. *Phys. Rev. B* **2008**, *77*, 214103.

(40) Hansen, P. E.; Bolvig, S.; Wozniak, K. *J. Mol. Struct.* **2005**, *749*, 155–168. Abildgaard, J.; Bolvig, S.; Hansen, P. E. *J. Am. Chem. Soc.* **1998**, *120*, 9063–9069. Korp, J. D.; Bernal, I.; Lemke, T. L. *Acta Crystallogr.* **1980**, *B36*, 428–434. Csöregh, I.; Norrestam, R. *Acta Crystallogr.* **1976**, *B32*, 2450–2455.

5 and **6** is due to the electrostatic repulsion between the two carboxylate anions in **6**. This destabilization is relieved in monoanion **5** by inserting a proton between the carboxylates. A similar relief of "strain" was proposed to account for the high basicity of 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene (**7**, X = OCH_3).[41] Nevertheless this relief of strain does not lead to a symmetric H-bond. Nor can the high ΔpK_a be attributed to an unusual strength of its H-bond, for which there is no independent evidence.



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Finally, and as an aside, we reject the proposal that "spurious cooperativity" is responsible for the large ΔpK_a in α,α′-dialkylsuccinic acids.[42] Instead we note that a defect of that argument is that it requires nearly equal populations of conformers with alkyls anti and gauche and with a high barrier to their interconversion by C−C rotation.

Conclusions

The monopotassium salt of (±)-α,α′-di-*tert*-butylsuccinic-^{18}O acid in three different solvents shows an isotope shift that is larger than the intrinsic isotope shift measured in the diacid, owing to perturbation of an equilibrium. Therefore hydrogen (±)-α,α′-di-*tert*-butylsuccinate monoanion **5** exists as a pair of interconverting tautomers rather than as a single symmetric structure. The asymmetry is attributed to interactions with the local environment, which is disordered, leading to solvatomers. The short O−O distance of 2.41 Å in **5** would suggest the formation of a short, strong H-bond, but **6** shows the same O−O distance, which therefore is mandated by the crystal and cannot be used as evidence for a strong H-bond. Moreover, it is not a symmetric H-bond, and there is no evidence for any special stabilization associated with symmetric H-bonds. The large ΔpK_a in **4** is therefore not due to any feature of the H-bond itself but is attributed to the electrostatic repulsion between the carboxylates in dianion **6**, which is relieved in monoanion **5** by inserting a proton between the carboxylates.

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Supporting Information Available: Synthetic Procedures, Spectral Characterizations, and Diffraction Techniques. Table S1 summarizing crystallographic data for α,α′-di-*tert*-butylsuccinic acid and six of its salts. Figure S1 of ^{13}C NMR spectra displaying the isotope shifts in (±)-α,α′-di-*tert*-butylsuccinic-^{18}O diacid and monoanion. Table S2 compiling ΔpK_a and O−O distances in dicarboxylate monoanions. Figure S2 showing the lack of correlation between ΔpK_a and O−O distance in dicarboxylate monoanions. X-ray crystallographic files in CIF format for the substances in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(41) Alder, R. W. *Chem. Rev.* **1989**, *89*, 1215–1223. Staab, H. A.; Saupe, T. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 865–879. Perrin, C. L.; Ohta, B. K. *J. Am. Chem. Soc.* **2001**, *123*, 6520–6526.

(42) Ben-Naim, A. *J. Chem. Phys.* **1998**, *108*, 3630–3647.