SUPPORTING INFORMATION FOR

Asymmetry of the "Strongest" OHO Hydrogen-Bond, in the Monoanion of (±)-α,α'-Di-*tert*-butylsuccinate

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Experimental

Reagents. Reagents, solvents, and NMR solvents were commercially available and were used as provided. Water-^{18}O (97 atom % ^{18}O) was commercially available through Sigma-Aldrich. NMR spectra were obtained on Varian Mercury 300, Mercury 400, and Unity 500 spectrometers. Spectra for the measurement of the isotopic perturbation of equilibrium were recorded with the default number of data points increased by a factor of 4 to reduce the error introduced by digitization. Mass spectra were obtained using a Thermo LCQdeca mass spectrometer with ESI source.

Monoethyl *tert*-butylmalonate was prepared by half hydrolysis of the diethyl ester using one equivalent of KOH. A mixture of stereoisomers of α,α'-di-*tert*-butylsuccinate diethyl ester was prepared by Kolbe electrolysis of the malonate monoester. Hydrolysis of the latter diester under acidic conditions yielded a mixture of α,α'-di-*tert*-butylsuccinic acid stereoisomers. Heating the mixture of stereoisomers in hot ethyl acetate gave the cyclic anhydride of (±)-α,α'-di-*tert*-butylsuccinic acid (**4**), along with meso α,α'-di-*tert*-butylsuccinic acid, which crystallized from solution upon cooling. The anhydride was isolated by concentration of the ethyl acetate filtrate to dryness. The anhydride was then hydrolyzed under basic conditions in a Na^{18}OH solution prepared by the addition of sodium hydride to $H_2{}^{18}O$ to give α,α'-di-*tert*-butylsuccin-^{18}O-ate (**6**-^{18}O). The α,α'-di-*tert*-butylsuccinic ^{18}O-acid (**4**-^{18}O) was isolated from aqueous solution by precipitation with HCl. Incorporation of a single oxygen-18 isotope was confirmed by mass spectroscopy. The hydrogen α,α'-di-*tert*-butylsuccin-^{18}O-ate monoanion (**5**-^{18}O) was generated by treating the diacid with one equivalent of potassium acetate. The methanol-soluble potassium

hydrogen α,α'-di-*tert*-butylsuccinate was isolated by concentrating the solution to dryness and the solid residue was washed with ether to remove acetic acid.

Monoethyl *t*-butylmalonate. Diethyl *t*-butylmalonate (10.0 g, 0.0473 mol) was dissolved in 20 mL ethanol, to which a solution of 3.1 g 85% KOH (0.047 mol) in 20 mL ethanol was added drop wise over 15 minutes. The solution was diluted with 15 mL H_2O and ethanol was removed by distillation. The aqueous solution was washed with 2 x 10 mL ether and acidified with HCl, rendering the monoethyl ester immiscible. The ester was isolated by extracting the mixture twice with 10 mL ether. The ether extract was washed twice with 10 mL H_2O and dried with $MgSO_4$ and then the ether was removed by distillation at 50 torr. The product oil was used without purification. Yield 8.576 g (0.047 mol), 100%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.13 (s, 9 H), 1.23 (t, 3 H), 3.25 (s, 1 H), 4.14 (q, 2 H), 11.1 (broad, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 6.85, 13.8, 27.6, 33.0, 60.7, 168.5, 169.0.

Diethyl α,α'-di-*tert*-butylsuccinate.[1] Monoethyl *t*-butylmalonate (8.570 g, 0.0468 mol) was dissolved in a solution of sodium methoxide (0.2561 g, 4.743 mmol) in 20 mL methanol in an ice bath. Platinum electrodes were immersed in the solution and a 0.1-A current from an Elenco Electronics XP-581 power supply was applied until the evolution of gas was no longer visible. The reaction mixture was then diluted with 10 mL H_2O and concentrated under reduced pressure to remove methanol. The aqueous solution was extracted with 2 x 10 mL ether. The ether extract was rotovaped to dryness to yield a mixture of stereoisomers of diethyl α,α'-di-*tert*-butylsuccinate. A 6:5 ratio of stereoisomers was indicated by NMR integration. The major stereoisomer was assigned as meso based on comparison with the chemical shifts of the separated diacids. Yield 4.194 g (0.0146 mol), 62.4%, mp 32-57 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (s, 18 H), 1.01 (s, 18 H), 1.25 (t, 6 H), 1.28 (t, 6 H), 2.46 (s, 2 H), 2.67 (s, 2 H), 3.99-4.21 (m, 8 H)

(±)-α,α'-Di-*tert*-butylsuccinic anhydride. Diethyl α,α'-di-*tert*-butylsuccinate (4.194 g, 0.0146 mol) was combined with 5 mL sulfuric acid and heated at 80 ºC for 5 min. The solution was cooled to room temperature. Dilution with 15 mL H_2O resulted in precipitation of both diastereomers of α,α'-di-*tert*-butylsuccinic acid, which was collected by vacuum filtration. The

meso α,α'-di-*tert*-butylsuccinic acid was precipitated from ethyl acetate-hexane. Meso α,α'-di-*tert*-butylsuccinic acid. Yield 1.0 g (4.3 mmol), 29% isolated yield, mp > 280 ºC (lit.[49] 310-312 ºC). ^{1}H NMR (500 MHz, CD_3OD): δ 0.87 (s, 18 H), 2.54 (s, 2 H).

The filtrate was concentrated to dryness to give (±)-α,α'-di-*tert*-butylsuccinic anhydride. Yield 0.868 g (4.09 mmol), 27.8% isolated yield, mp 111-112 ºC (lit.[49] 114-115 ºC). ^{1}H NMR (500 MHz, CD_3OD): δ 1.05 (s, 18 H), 2.59 (s, 2 H).

(±)-α,α'-Di-*tert*-butylsuccinic acid (4). (±)-α,α'-Di-*tert*-butylsuccinic anhydride (0.248 g, 1.17 mmol) was added to 1 mL 1 M NaOH and heated at reflux until the anhydride dissolved. The solution was cooled to r.t., and acidified with concentrated HCl to precipitate (±)-α,α'-di-*tert*-butylsuccinic acid. Yield 0.234 g (1.1 mmol), 94%, mp 149-152 ºC (lit.[49] 151-152 ºC). ^{1}H NMR (300 MHz, CD_3OD): δ 1.06 (s, 18 H), 2.57 (s, 2 H). MS (ESI in methanol) calc. for C12H21O4 (M-H), 229.14; found 229.06. The diacid could be recrystallized from aqueous acetone at 0 C.

(±)-α,α'-Di-*tert*-butylsuccinic [^{18}O]acid (4-^{18}O). Powdered sodium hydride (10 mg, 0.43 mmol) was added to 50 μL water-^{18}O (97 atom % ^{18}O). Hydrogen gas evolved from the reactions was flushed from the reaction vessel using a gentle stream of nitrogen. (±)-α,α'-Di-*tert*-butylsuccinic anhydride (32.1 mg, 0.151 mmol) was added to the $Na^{18}OH_{(aq)}$ solution. The reaction vessel was sealed and heated to 45 ºC. Reaction completion after 5 min was determined by ^{13}C NMR analysis of an aliquot. Dropwise addition of 1M HCl resulted in the precipitation of (±)-α,α'-di-*tert*-butylsuccinic acid. The precipitate was collected by filtration and dried in air. Yield 29.3 mg (0.126 mmol), 83.4 %, mp 151-152 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (s, 18 H), 2.55 (s, 2 H), 8.95 (broad, 2 H). (400 MHz, CD_3OD): δ 1.05 (s, 18 H), 2.52 (s, 2 H). (400 MHz, acetone-d_6): δ 1.05 (s, 18 H), 2.54 (s, 2 H), 6.36 (s, 1 H). (400 MHz, THF-d_8): δ 1.04 (s, 18 H), 2.29 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.39, 34.56, 54.69, 179.60. (100 MHz, CD_3OD): δ 27.39, 33.73, 54.25, 176.75. Selected ^{13}C NMR (100 MHz, acetone-d_6): δ 175.20. ^{13}C NMR (100 MHz, THF-d_8): δ 28.85, 33.69, 58.85, 182.88. MS (ESI in methanol) calc. for $C_{12}H_{21}O_3{}^{18}O$ (M-H), 231.15; found 231.06.

Potassium hydrogen (±)-α,α'-di-*tert*-butylsuccin[^{18}O]ate (5-^{18}O). Di-*tert*-butylsuccinic [^{18}O]acid (29.3 mg, 0.126 mmol) was dissolved in 1 mL methanol. Potassium acetate (12.4 mg, 0.126 mmol) was added to the solution. The solution was allowed to evaporate and the residue was washed with ether to remove acetic acid. Yield 34.0 mg (0.126 mmol), 99.6%. ^{1}H NMR (400 MHz, CD_3OD): δ 1.06 (s, 18 H), 2.50 (s, 2 H). (400 MHz, acetone-d_6): δ 1.03 (s, 18 H), 2.41 (s, 2 H), 18.78 (broad, 1 H). (400 MHz, THF-d_8): δ 1.04 (s, 18 H), 2.29 (s, 2H). ^{13}C NMR (100 MHz, CD_3OD): δ 28.72, 33.20, 56.64, 180.02. (100 MHz, acetone-d_6): δ 29.41, 33.16, 57.10, 177.93, (100 MHz, THF-d_8): δ 30.08, 34.93, 60.02, 183.95. Figure S1 shows the carboxyl region of the ^{13}C NMR spectra, displaying the isotope shifts in diacid and monoanion.

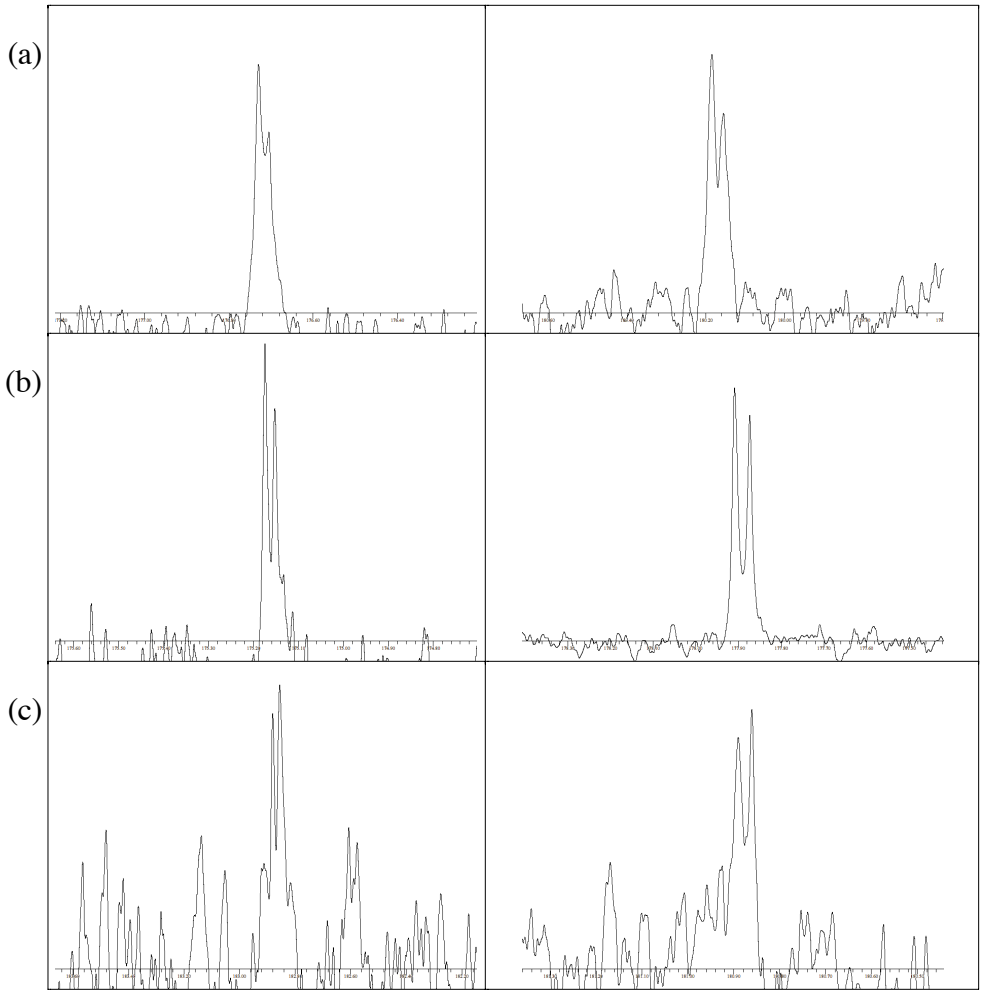

Figure S1. Carboxyl region of ^{13}C NMR spectra of mono-^{18}O-labeled (±)-α,α'-di-*tert*-butylsuccinic acid (at left) and its monoanion (at right) in (a) CD_3OD, (b) acetone-d_6, and (c) THF-d_8. Scan = 0.9-1.4 ppm.

Hydrogen (±)-α,α'-di-*tert*-butylsuccinate, tetramethylammonium salt. (±)-α,α'-Di-*tert*-butylsuccinic acid (80.7 mg, 0.35 mmol) was dissolved in 126 μL of a 25% w/w $Me_4NOH_{(aq)}$ solution (0.35 mmol). The solution was concentrated under vacuum to give a yellow oil. The oil was dissolved in ethanol and the solvent was allowed to evaporate to give a solid residue. This residue was recrystallized successively from methylene chloride and THF to give needle-like crystals. Yield 100 mg (0.33 mmol), 94%, mp 92-95 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.01 (s,

18 H), 2.45 (s, 2 H), 3.35 (s, 12 H). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.93 (s, 18 H), 2.18 (s, 2 H), 3.09 (s, 12 H), 19.55 (s, 1 H).

Hydrogen (±)-α,α'-di-*tert*-butylsuccinate, tetraethylammonium salt. (±)-α,α'-Di-*tert*-butylsuccinic acid (29 mg, 0.126 mmol) was dissolved in 53 μL of a 35% w/w $Et_4NOH_{(aq)}$ solution (0.13 mmol). The solution was concentrated under vacuum to give a yellow oil. Crystallization of this oil was unsuccessful. Yield 45.2 mg (0.120 mmol), 95%. ^{1}H NMR (500 MHz, CD_3OD): δ 0.97 (s, 18 H), 1.19 (tt, 12 H), 2.41 (s, 2 H), 3.21 (q, 8 H).

Hydrogen (±)-α,α'-di-*tert*-butylsuccinate, tetrapropylammonium salt. (±)-α,α'-Di-*tert*-butylsuccinic acid (43.4 mg, 0.189 mmol) was dissolved in 190 μL of a 1.0 M $Pr_4NOH_{(aq)}$ solution (0.19 mmol). The solution was concentrated under vacuum to give 79.6 mg of a yellow oil, which was taken up in benzene, from which small white plates could be crystallized and then recrystallized successively from THF and toluene by slow evaporation to give blade-like crystals suitable for diffraction analysis. Yield 35 mg (0.084 mmol), 45 %, mp 150-151 ºC. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.88 (t, 12 H), 0.92 (s, 18 H), 1.60 (m, 8 H), 2.18 (s, 2 H), 3.11 (m, 12 H), 19.53 (s, 1 H).

Hydrogen (±)-α,α'-di-tert-butylsuccinate, tetrabutylammonium salt. (±)-α,α'-Di-tert-butylsuccinic anhydride (49.0 mg, 0.23 mmol) was added to 230 ml of a 1M aqueous Bu_4NOH solution (0.23 mmol). The mixture was heated until the anhydride was dissolved and the water was slowly evaporated in the vacuum oven at 50 ºC to give hygroscopic needle-like crystals.

Hydrogen (±)-α,α'-di-tert-butylsuccinate, tetrabutylphosphonium salt. (±)-α,α'-Di-tert-butylsuccinic anhydride (46.6 mg, 0.22 mmol) was added to the solution of 150 ml of a 40 wt % aqueous Bu_4POH (0.22 mmol) and 140 ml deionized water. The mixture was heated until the anhydride was dissolved. After cooling, the white solid was collected from the top layer of the solution. The solid was recrystallized from benzene to give needle-like crystals. mp 176-178 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (t, 12 H), 1.08 (s, 18 H), 1.46-1.56 (m, 16 H), 2.28-2.38 (m, 8 H), 2.49 (s, 2 H), 19.6 (s, 1 H).

Magnesium and calcium bis(hydrogen (±)-α,α'-di-tert-butylsuccinate). Reaction of the diacid with one equivalent of MgO in water or of $MgCl_2$ + NaOH in aqueous isopropanol and evaporation of solvent did not produce the expected salt of the dianion, but rather the hexaaquomagnesium salt of the bis(hydrogen di-*tert*-butylsuccinate monoanion), with one water of crystallization. Similarly the tetraaquocalcium salt was obtained, also with one water of crystallization.

Dicesium (±)-α,α'-di-tert-butylsuccinate. The cesium salt of the dianion was obtained by heating the aqueous diacid at 90ºC with one molar equivalent of Cs_2CO_3 and evaporating the water, to produce rods of the trihydrate.

Diffraction Techniques. Single-crystal X-ray diffraction studies were carried out on either a Bruker Platform D8 APEX CCD diffractometer equipped with Mo K_α radiation (λ = 0.71073Å) or a Bruker Kappa APEXII CCD diffractometer equipped with Cu K_α radiation (λ = 1.5478Å). The crystals were affixed to a Nylon cryoloop using oil (Paratone-*n*, Exxon) and mounted in the cold stream of the diffractometer. The temperature at the crystal was maintained at the specified temperature using either a Cryostream 700EX cooler (Oxford Cryosystems) for the Cu data collections or a Kryo-Flex (Bruker-AXS) for the Mo data collections. Data collection, reduction, structure solution, and refinement were performed using the Bruker Apex2 suite. All available reflections to $2\theta_{max}$ were harvested and corrected for Lorentz and polarization factors with Bruker SAINT. Reflections were then corrected for absorption, interframe scaling, and other systematic errors with SADABS 2008/1. The structure was solved (direct methods) and refined (full-matrix least-squares against F^2) with the Bruker SHELXTL package. All non-hydrogen atoms were refined using anisotropic thermal parameters. All CH and H_2O hydrogens were fixed at idealized positions, but OH positions in the intramolecular hydrogen bond were refined.

Computations. Because the crystals of the diacid are partially disordered, distances and angles from its X-ray structure may not be reliable. Therefore the diacid was also modeled with the MM2 force field of CambridgeSoft's Chem3D Version 4.0.

Table S1. Crystallographic data for tetrapropylammonium, tetrabutylammonium, and tetrabutylphosphonium (±)-α,α'-di-*tert*-butylsuccinates (**5**).

formula	$C_{24}H_{51}NO_5$	$C_{28}H_{57}NO_4$	$C_{28}H_{57}O_4P$
a, Å	19.615	13.095	13.0862
b, Å	16.4013	13.9148	15.4546
c, Å	17.4466	16.7377	15.2946
α, deg	90.00	90	90
β, deg	99.925	96.29	96.136
γ, deg	90.00	90	90
V, Å^3	5528.8	3031.5	3075.5
Z	8	4	4
fw	433.66	471.75	488.71
space group	P2(1)/c	Pn	P2(1)/n
T, K	223	100	123
λ, Å	0.71073	0.71073	0.71073
d, g cm^{-3}	1.042	1.034	1.055
μ, mm^{-1}	0.071	0.067	0.117
$R(F_o)$, all data	0.1256	0.0820	0.1566
$R(F_o)$, $I > 2\sigma(I)$	0.0649	0.0678	0.1038
$R_w(F_o^2)$, all data	0.1958	0.1855	0.3391
$R_w(F_o^2)$, $I > 2\sigma(I)$	0.1627	0.1718	0.2889

Table S1,ctd. Crystallographic data for magnesium$_{1/2}$ and calcium$_{1/2}$ hydrogen (±)-α,α'-di-*tert*-butylsuccinates (**5**), for dicesium (±)-α,α'-di-*tert*-butylsuccinate (**6**), and for (±)-α,α'-di-*tert*-butylsuccinic acid (**4**).

formula	$C_{24}H_{58}MgO_{15}$	$C_{24}H_{54}CaO_{14}$	$C_{24}H_{46}Cs_2O_{11}$	$C_{12}H_{22}O_4$ (**4**)
a, Å	6.3954	6.4772	12.681	35.565
b, Å	31.990	14.484	16.709	7.514
c, Å	16.2225	17.584	15.323	10.398
α, deg	90	90	90	90
β, deg	97.990	92.390	103.387	106.706
γ, deg	90	90	90	90
V, Å^3	3286.8	1648.2	3158.5	2661.45
Z	4	2	4	8
fw	596.90	606.75	776.43	230.30
space group	Cc	P2(1)/n	P2(1)/n	C2/c
T, K	100	150	100	120
λ, Å	1.54178	0.71073	1.54184	1.54178
d, g cm^{-3}	1.206	1.223	1.633	1.149
μ, mm^{-1}	1.017	0.249	18.431	0.694
$R(F_o)$, all data	0.0470	0.0499	0.0531	0.0824
$R(F_o)$, $I > 2\sigma(I)$	0.0460	0.0431	0.0448	0.0757
$R_w(F_o^2)$, all data	0.1207	0.1003	0.1151	0.2028
$R_w(F_o^2)$, $I > 2\sigma(I)$	0.1194	0.0972	0.1102	0.1994

Table S2. Diacid monoanions with short intramolecular H-bonds.

Diacid	pK_{a1}[a]	pK_{a2}[a]	ΔpK_a	counterion	$d_{O\text{-}O}$	Ref
Difluoromaleic			?	K^+	2.415	2
Benzene-1,2,4,5-tetracarboxylic	2.87	4.49	1.62[b]	$(H_2O)_2Na^+{}_2$	2.396	3
				$(H_2O)_6Zn^{++}$	2.415	3
Chloromaleic	1.72	3.86	2.14	K^+	2.40	4
Phthalic	2.98	5.28	2.30	$H_2O\text{-}Li^+$	2.400	5
				$CH_3OH\text{-}Li^+$	2.390	6
				$(H_2O)_2Cu^{++}$	2.391	7
				$(thiourea)_3Cu^+$	2.351	8
				$(C_2H_5)_4N^+$	2.374	9
				$(n\text{-}C_4H_9)_4N^+$	2.385	9
				$^1/_2(H_2O)_6Co^{++}$	2.384	10
				$^1/_2(H_2O)_6Mg^{++}$	2.38	11
				$^1/_2(CH_3OH)_2(H_2O)_4Mg^{++}$	2.397	12
				2,6-Dimethylpyridinium	2.398	13
Cyclobutane-1,1-dicarboxylic[c]	3.13	5.88	2.75	K^+	2.53	14
Maleic	1.93	6.58	4.65	$Imidazolium^+$	2.393	15
				K^+	2.427	16
				Li^+	2.46	17
				$HOCOCH_2N(CH_3)_3^+$	2.429[b]	18
				$CH_3NH_3^+$	2.421	19
				$CH_3NH_3^+$	2.418	19
Cyclopropane-1,1-dicarboxylic[c]	1.82	7.43	5.61	Na^+	2.429	20

[a]From Ref. 21. [b]pK_{a3} - pK_{a2}. [c]From Ref. 22.

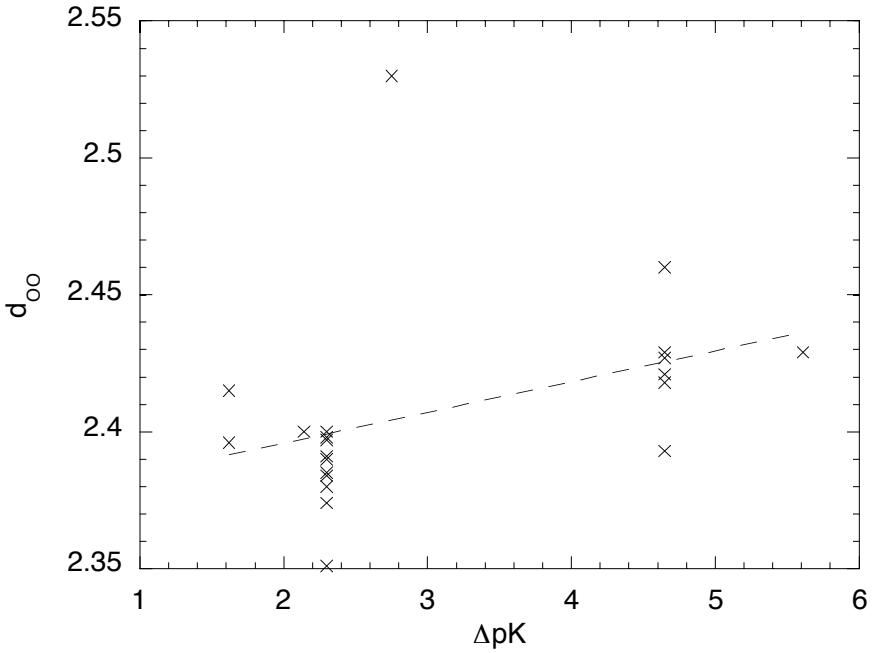

Figure S2. Lack of correlation ($\rho = 0.39$) between ΔpK_a and O-O distance in dicarboxylate monoanions.

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