Synthesis and Conformational Analysis of *cis,cis*-1,3,5-Trimethylcyclohexane-1,3,5-tricarboxylic Acid

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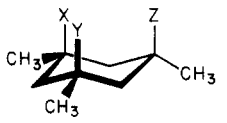
Conversion of 3,5,7-trimethyladamantan-1-ol to a hypobromite, fragmentation in situ, and oxidation with $KMnO_4$ generate the lactone, **6**, of *cis,cis*-1,3,5-trimethyl-1-(hydroxymethyl)cyclohexane-3,5-dicarboxylic acid, which can in turn be oxidized by RuO_4–HIO_4 to *cis,cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylic acid (**2**). From pK_a measurements and ^1H NMR studies, **2** and its mono- and dianions are assigned chair conformations with the functional groups triaxial. The trianion of **2** is assigned the chair conformation with triequatorial carboxylate anions. Conversion of **6** to the lactone, **8**, of *cis,cis*-1,3,5-trimethyl-1-formyl-3-(hydroxymethyl)cyclohexane-5-carboxylic acid and **2** to the cyclic anhydride, **11**, of *cis,cis*-1,3,5-trimethyl-1-formylcyclohexane-3,5-dicarboxylic acid by Rosenmund reduction is described.

Proximity effects can result in dramatic changes in functional group behavior which have provided many speculative models for enzymatic catalysis.[1] Most such models have involved pairs of proximate functional groups, and we were therefore attracted to the general cyclohexane structure **1** which positions three functional groups at an



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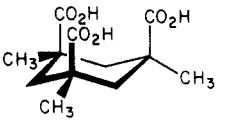
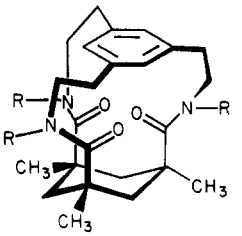


2



3

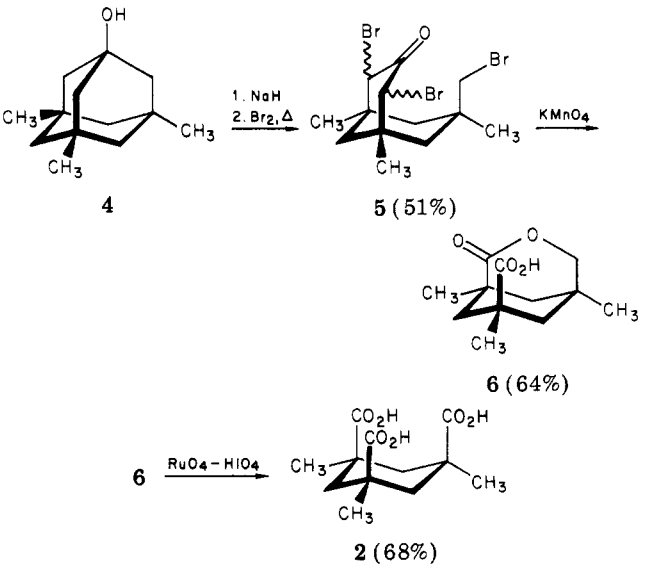
~0.25-nm separation. In this paper we report convenient syntheses of *cis,cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylic acid (**2**) as well as several of its reduction products. We also present pK_a and ^1H NMR evidence in support of the assignment of a triaxial orientation for the carboxyl groups of **2**. In addition to allowing study of proximity effects of three functional groups, **1** and **2** may provide access to novel cage-type structures such as **3**.

Synthesis

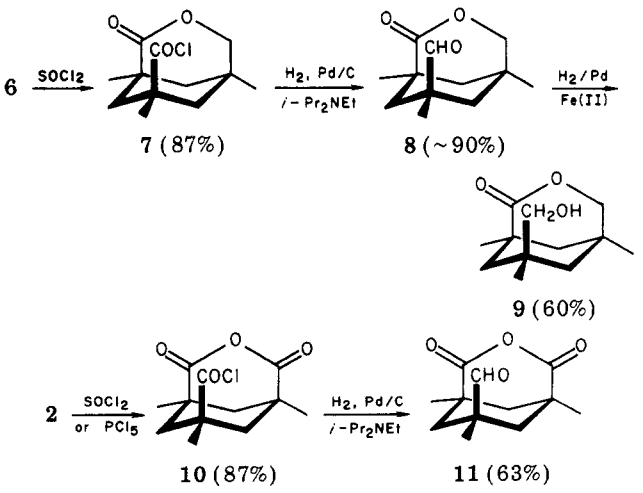
As shown in Scheme I, **2** can be prepared in three steps in an overall yield of 22% by an oxidative degradation of 3,5,7-trimethyladamantan-1-ol (**4**), which is available commercially. Although a one-pot degradation of **4** to **2** can also be envisaged, thus far we have been unable to realize it.

Fragmentation of an initially formed hypobromite parallels related fragmentations reported by Black and Gill[2] and by Lunn[3] for 1-adamantanol and forms a cyclohexanone which undergoes α bromination under the reaction conditions to form **5**. Although this substance can also be oxidized in 64% yield to **6** by means of chromium trioxide in hot acetic acid–perchloric acid, more convenient

Scheme I



Scheme II



conditions involve potassium permanganate in water–pyridine. Conversion of the resulting lactone–acid **6** to **2** can then be effected by a catalytic amount of ruthenium dioxide in the presence of periodic acid. The structure of **2** is established most convincingly by its ^1H NMR spectrum, which shows the four resonances expected for this trisymmetric molecule.

Three of the derivatives of general structure **1** in which X, Y, and Z are primary alcohol, aldehyde, and/or car-

(1) For a recent discussion, see: Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *23*, 183–278.
(2) Black, R.; Gill, G. *J. Chem. Soc., Chem. Commun.* **1970**, 972.
(3) Lunn, W. *J. Chem. Soc. C* **1970**, 2124.

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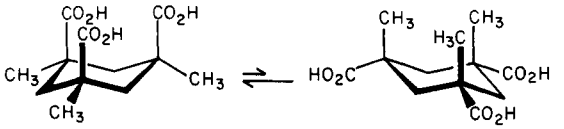
boxylic acid functions have been prepared by the reaction sequences of Scheme II. Interestingly, the anhydride–acid chloride **10** is isolated as the sole product of reactions between thionyl chloride or phosphorus pentachloride and **2** under a variety of conditions.

Probable Structure for 2 and Its Trianion

Of the two chair conformations available to **2**, **12**, in which the three carboxyl groups are oriented triaxially, is likely to be more stable than **13**. Although *A* values alone



12 **13**

are likely to provide only a crude approximation in cases involving 1,3-diaxial interactions, it is noteworthy that methyl shows a significantly larger *A* value than carboxyl.[4] More cogently, it is evident from space-filling models that relatively flat carboxyl groups can pack in a triaxial array with less crowding than three methyl functions, and intramolecular hydrogen bonding is likely to enhance this bias.

On the other hand, the polyanions derived from **2** might be expected to show the reverse conformational preference. Successive ionization of the carboxylic acid groups of **2** forms species which must be destabilized by electrostatic repulsion in the chair conformation with triaxial carboxylates. Either the dianion or the trianion of **2** might therefore assume the triequatorial conformation as its more stable orientation.[5] It is interesting to note that a rapid conformational change which affects the binding constant at each of several identical reactive sites is the defining feature of the concerted model for allosteric proteins.[6] Provided the constants of dissociation and conformational change for **12** and **13** have the right magnitude, **2** [or related species such as the triamine **1** (X = Y = Z = NH_2)] might be a very simple working model for an allosteric effect. As will be noted, this effect is not seen for **2**, but it remains a possibility for the triamine.

Conformational assignments for highly substituted, nonrigid cyclohexane derivatives can be subject to major uncertainties.[7] Even in cases for which an X-ray analysis has provided a structure in the crystal, it can be argued that differences between lattice and solvation energies can result in a different conformational preference in solution. The most convincing structural assignment for the latter involves finding conformation-sensitive properties which are identical with those seen for models with rigid, known structures.

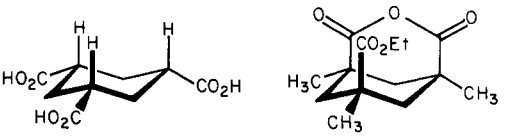
A candidate for such a property is the very large difference in chemical shift (δ 1.5–1.7) which is seen for the resonances of the nonequivalent methylene hydrogens of **2** and its triester (Table I; entries **1a,b** and **2a,b**). This difference is largely attributable to the anisotropy of the carbonyl groups of **2** and its derivatives. It is only consistent with a preferred conformation for **2** in which the two methylene hydrogens experience, on the average, a very different orientation with respect to the neighboring acyl functions. Conformation **13**, with equal distances between carboxyl and methylene hydrogens, can therefore be described as a minor contributor to **2**, and, with somewhat less assurance, boat or twist-boat conformation, which must rapidly average the methylene–carboxyl interactions of **12** and **13**, can also be excluded.

Table I. ^{1}H Chemical Shift Values

entry	structure (solvent)[a]	chemical shift, δ CH_3C	chemical shift, δ CH_2	Δ_{CH_2}[b]
1a	2	1.23	ca. 1.2,[c] 2.63	
b	2 (CD_3OD)	1.25	1.20, 2.70	1.50
c	2, monosodium salt	1.20	1.13, 2.54	1.41
d	2, disodium salt	1.20	1.15, 2.47	1.32
e	2, trisodium salt	1.30	1.50, 2.10	0.60
2a	2, trimethyl ester (CD_3OD)	1.20	1.10, 2.70	1.60
b	2, trimethyl ester ($CDCl_3$)	1.20	1.00, 2.70	1.70
3a	14		1.41, 2.22	0.81
b	14, trisodium salt		1.37, 2.01	0.64

[a] Unless specified, the solvent is 1:1 CD_3OD–D_2O. [b] Δ_{CH_2} = difference in chemical shift values for axial and equatorial methylene protons in parts per million. [c] Resonance masked by absorption due to methyl groups.

More rigorous evidence for these conclusions is available from models. The ring-locked species **6**, **7**, and **15** ap-



14 **15**

proximate the methylene–carboxyl environment of **12**, in which the most deshielded methylene hydrogen is flanked by a pair of axial acyl functions. Species **14** can be taken as a model for the triequatorial environment of **13**, in which the two methylene hydrogens are nearly equidistant from the acyl groups. Strikingly, **6**, **7**, and **15** all show (see Experimental Section) differences in methylene chemical shift (δ 1.3–1.6) and anomalously deshielded methylene hydrogens (δ 2.7) that correspond exactly to those observed for **2**. On the other hand, **14** and its trianion (Table I, entries **3a,b**) show the normal difference of methylene chemical shift (δ 0.6–0.8) that is seen for simple cyclohexane derivatives.[7]

The chemical shifts seen for a mixture of rapidly equilibrating conformations of comparable stability must correspond to a weighted average of chemical shifts for the individual conformations. The near identity of methylene spectra for the rigid models and for **2** provides compelling support for assignment of the triaxial structure **12** to the triacid.

As seen in Table I (entry **1e**) the proton resonances for the methylenes of the trianion of **2** are separated by only δ 0.6 and are similar to those of **14** and its trianion but unlike those of the rigid models. Formation of the trianion is therefore accompanied by a change in conformation, and the chair form with the three carboxylate functions triequatorial is most consistent with the observations, although a contribution of twist-boat forms probably cannot be excluded.

The pK_a date of Table II are in complete accord with this conformational picture. A symmetrical, unhindered,

(4) Hirsch, J. A. *Top Stereochem.* **1967**, *1*, 204–8.

(5) It might be argued that **2** or its trianion assume boat or twist-boat conformations. A peculiarity of a 1,3,5 geminally trisubstituted cyclohexane makes this possibility appear unlikely to us: the closest H–H distance of the methyls of **13** and the analogous H–H distance for the flagpole interaction of a boat conformation are identical, and similar identities can be found in a twist-boat conformation. Although we have not made quantitative energy estimates to confirm this point, it seems likely that the effect of substitution is to raise the energies of all three types of cyclohexane conformations equally.

(6) Monod, J.; Wyman, J.; Changeux, J.-P. *J. Mol. Biol.* **1965**, *12*, 88.

(7) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed; Pergamon: Oxford, 1969; pp 238–40.

Table II. pK_a Values at 25 °C

	H_2O		CH_3OH-H_2O (1:1 v/v)	
substance	pK_a	Δ_{pK_a}[a]	pK_a	Δ_{pK_a}[a]
2	3.3		4.7	
		2.5		2.9
	5.85		7.6	
		1.5		1.2
	7.3		8.8	
14	3.8		5.0	
		0.7		0.7
	4.5		5.7	
		0.7		0.7
	5.2		6.4	
6			6.3	

[a] Difference between pK_a values for successive dissociations.

aliphatic tricarboxylic acid with no inductive interactions between its acidic groups is expected to exhibit three pK_a values centered at about 4.7 and separated by a statistical factor of log 3 = 0.5. This limiting behavior is approached by the pK_a values observed for **14**.

An acid with neighboring ionizable groups is expected to show a much larger separation between pK_a values. An example is phthalic acid, for which the pK_as for the first and second dissociations are separated by 2.5.[8] Although part of this difference is probably due to stabilization of the monoanion through intramolecular hydrogen bonding, the larger part can be attributed to destabilizing charge repulsion in the dianion.

As seen from Table II, the first two pK_a values of **2** are separated by 2.5 pK_a units, as expected for a triacid and its monoanion with proximate carboxylate functions as in **12**. Were this triaxial orientation shared with the trianion of **2**, one would expect at least as large a separation between the second and third pK_a values, resulting from the destabilizing effect of additional charge density. The smaller separation that is observed is only in accord with a conformational change that separates the three negative charges of the trianion.

Even though the trianion of **2** is less basic than one would expect if it assumed the triaxial chair conformation, it still may hold the record for the most basic example of a carboxylic acid anion. Even the hexaanion of benzene-1,2,3,4,5,6-hexacarboxylic acid is a weaker base (pK_{a-6} = 6.76).[9]

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian T-60 or a Hitashi Perkin-Elmer R-24B spectrometer. IR spectra were obtained by using a Perkin-Elmer 283-B or 567 instrument. Elemental analyses were performed by Midwest Microlab, Ltd.

Organic phases obtained from aqueous extractions were dried over anhydrous sodium or magnesium sulfates and were evaporated in a Büchi rotary evaporator at water aspirator pressure. Benzene used in the conversion of **4** to **5** was distilled from calcium hydride and stored over 4-Å molecular sieves.

***cis,cis*-1,3,5-Trimethyl-1-(hydroxymethyl)cyclohexane-3,5-dicarboxylic Acid Lactone (6).** Sodium hydride (13.7 g of 59% oil suspension, 0.33 mol) was washed under nitrogen with benzene, suspended in 1400 mL of dry benzene, and treated with 3,5,7-trimethyladamantan-1-ol (8.56 g, 44.1 mmol); the resulting suspension was refluxed under nitrogen with stirring until gas evolution ceased (ca. 6 h). Solids were allowed to settle, and the supernatant phase was transferred by cannula to a dry nitrogen-filled flask with the help of hot, dry benzene (2 × 200 mL). To the resulting solution was added bromine (14.0 mL, 272 mmol, freshly distilled from barium oxide) with vigorous stirring which was continued for 3 h in the dark at 25 °C. The mixture was then brought to 65–70 °C, stirred under a reflux condenser for 13 h, cooled, and filtered to yield 12.0 g of sodium bromide. The filtrate was washed with a solution of 224 g of sodium iodide in 1800 mL of water, with 20% aqueous sodium thiosulfate (color discharged), with water (2 × 500 mL), and with brine. Drying and evaporation gave 15.4 g of crude product which was suspended in 50 mL of petroleum ether to yield 9.62 g (51%) of solid (mp 130–135 °C)3-(bromomethyl)-6,8-dibromo-1,3,5-trimethylbicyclo[3.3.1]-nonan-7-one (**5**).

Tribromo ketone **5** (9.55 g, 22.2 mmol) and potassium permanganate (81.4 g, 0.5 mol) in 1 L of water and 750 mL of pyridine were stirred vigorously in a bath at 85–100 °C for 5 h. The volatiles were then evaporated, and the resulting black solid was acidified with cold 6 N hydrochloric acid and treated with 6% sulfurous acid with cooling until a colorless solution was obtained. Chloroform (6 × 300 mL) was used for extraction, and the pooled extracts were washed with water and brine, dried, and evaporated to yield 4.25 g solid which was recrystallized (benzene) to give colorless crystals of *cis,cis*-1,3,5-trimethyl-1-(hydroxymethyl)-cyclohexane-3,5-dicarboxylic acid lactone (**6**): mp 221–224 °C; 3.15 g (64%); IR (KBr) 3100, 1710 cm^{-1}; mass spectrum, *m/e* 226 (M^+); ^1H NMR ($CDCl_3$) δ 0.93 (s, 3 H), 1.23 (s, 3 H), 1.26 (s, 3 H), 0.8–1.5 (m, 3 H), 1.80 (d, *J* = 13 Hz, 1 H), 2.60 (d, *J* = 14 Hz, 2 H), 3.95 (dd, *J* = 12, 2 Hz, 1 H), 4.31 (dd, *J* = 12, 2 Hz, 1 H), 8.8 (s, 1 H).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.72; H, 7.96. Found: C, 63.52; H, 7.81.

***cis,cis*-1,3,5-Trimethylcyclohexane-1,3,5-tricarboxylic Acid (2).** The lactone carboxylic acid **6** (1.83 g, 8.1 mmol) in 50 mL of water containing sodium hydroxide (0.68 g, 17.2 mmol) was heated at 90 °C for 30 min and then cooled. The solution was brought to pH 8.0 with hydrochloric acid, treated with a catalytic amount of ruthenium dioxide (ca. 5 mg), and stirred vigorously as sodium periodate as a 5% aqueous solution (3.87 g, 16.2 mmol) was added at a rate sufficient to barely maintain the yellow color (ca. 3.5 h required). After a further 2.5 h the dioxide color was quenched with 2-propanol, and the black suspension was acidified to pH 1 with hydrochloric acid and extracted with ethyl acetate (7 × 200 mL). The pooled extracts were washed with water and brine, dried, and evaporated to give a residue which was recrystallized from chilled acetone to yield the tricarboxylic acid **2**: mp 230–245 °C; 1.43 g (68%); IR (KBr) 3000, 1710, 1400, 900 cm^{-1}; mass spectrum, *m/e* 258 (M^+), 240 ($M^+ - H_2O$); ^1H NMR (pyridine-d_5) δ 1.5 (s, 9 H), 1.5 (d, *J* = 14 Hz, 3 H), 3.3 (d, *J* = 14 Hz, 3 H), 13.5 (s, 3 H).

Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 6.98. Found: C, 55.90; H, 6.96.

Reaction of the triacid **2** with excess ethereal diazomethane gave the trimethyl ester: mp 79–81 °C; ^1H NMR ($CDCl_3$) δ 0.95 (d, *J* = 13 Hz, 3 H), 1.20 (s, 9 H), 2.70 (d, *J* = 14 Hz, 3 H), 3.60 (s, 9 H).

Reaction of the triacid **2** with threefold excesses of diphenylphosphoryl azide and triethylamine in ethanol at reflux for 20 h gave the monoethyl ester of the cyclic anhydride **15**: 50%; mp 215–219 °C; ^1H NMR ($CDCl_3$) δ 1.1–1.6 (m, 15 H), 2.00 (d, *J* = 13 Hz, 1 H), 2.70 (d, *J* = 13 Hz, 2 H), 4.05 (d, *J* = 7 Hz, 2 H).

5-(Chloroformyl)-*cis,cis*-1,3,5-trimethyl-3-(hydroxymethyl)cyclohexane-1-carboxylic Acid Lactone (7). Lactone carboxylic acid **6** (50.2 mg, 0.22 mmol) was brought to reflux in thionyl chloride (1 mL) for 2 h. The residue obtained by evaporation was recrystallized from dry toluene–cyclohexane to yield **7**: 83.5 mg (82%); mp 169–170.5 °C; IR (Nujol) 1795, 1740 cm^{-1}; mass spectrum, *m/e* 244 (M^+), 246 ($M^+ + 2$); ^1H NMR ($CDCl_3$) δ 1.1–1.5 (m, 12 H), 1.8 (d, *J* = 14 Hz, 1 H), 2.6 (d, *J* = 14 Hz, 2 H), 4.05 (d, *J* = 12 Hz, 1 H), 4.20 (d, *J* = 12 Hz, 1 H).

Anal. Calcd for $C_{12}H_{17}O_3Cl$: C, 58.90; H, 6.95; Cl, 14.52. Found: C, 59.07; H, 6.92; Cl, 14.34.

5-(Chloroformyl)-*cis,cis*-1,3,5-trimethylcyclohexane-1,3-dicarboxylic Anhydride (10). By use of a procedure similar to the above, **2** was combined with thionyl chloride and allowed

(8) Kortüm, G.; Vogel, W.; Andrussow, K. "Dissociation Constants of Organic Acids in Aqueous Solution"; Butterworths: London, 1961; p 363.
(9) Reference 8, p 367.

to reflux for 4 h. Evaporation and crystallization from dry toluene gave 87% of **10**: mp 255–260 °C; IR (Nujol) 1780 cm^{-1}; mass spectrum, m/e 259 (M^+).

Anal. Calcd for $C_{12}H_{15}O_4Cl$: C, 55.71; H, 5.80; Cl, 13.73. Found: C, 55.88; H, 5.78; Cl, 13.80.

5-Formyl-*cis*,*cis*-1,3,5-trimethylcyclohexane-1,3-dicarboxylic Anhydride (11). A modified Rosenmund reduction was used, following the procedure of Peters et al.[10] A slurry of Pd/C (10%, 20–30 mg) in 2 mL of acetone containing 0.1 mL of diisopropylethylamine was stirred 1 h under hydrogen. Acid chloride **10** (53 mg, 0.20 mmol) was added, and hydrogenation was continued for 2 h at 1 atm of H_2 and 25 °C. After filtration and evaporation, the residue was dissolved in ethyl acetate, and the resulting solution was washed with 1 N hydrochloric acid (3 × 10 mL) and water (4 × 10 mL). Drying and evaporation gave a solid which was recrystallized twice from toluene: 35%; mp 276–277 °C. The substance was obtained as a mixture of the free aldehyde **11** and an isomer which is assigned a cyclic 1,1-dilactone structure: IR (Nujol) 1795, 1760, 1720 cm^{-1}; mass spectrum, m/e 196 (M^+ - CO); ^1H NMR (250 MHz in $(CD_3)_2CO$–$CDCl_3$) δ 1.0–1.6 (m, 12 H), 2.55 (d, J = 15 Hz, 3 H), 7.57 (s, 0.6 H), 9.32 (s, 0.4 H).

Anal. Calcd for $C_{12}H_{16}O_4 \cdot 0.4H_2O$: C, 62.30; H, 7.26. Found: C, 62.23; H, 6.76.

5-Formyl-*cis*,*cis*-1,3,5-trimethyl-3-hydroxymethylcyclohexane-1-carboxylic Acid Lactone (8). A procedure nearly identical with that outlined above was employed with the acid chloride **7** by using a hydrogenation time of 24 h. Recrystallization of the reaction residue from water gave 60% of formyl lactone **8**: mp 156.5–158 °C; IR (Nujol) 1715 cm^{-1}; mass spectrum, m/e 182 (M^+ - CO); ^1H NMR ($CDCl_3$) δ 0.9–1.5 (m, 12 H), 1.80 (d, J = 17 Hz, 1 H), 2.4 (d, J = 14, 2 H), 4.0 (d, 2 H), 9.5 (s, 1 H).

Anal. Calcd for $C_{12}H_{18}O_3 \cdot 0.25H_2O$: C, 67.15; H, 8.62. Found: C, 67.20; H, 8.65.

Hydrogenation of **8** in acetic acid over platinum oxide containing a trace of ferrous chloride for 24 h at 1 atm of H_2 and 25 °C gave lactone alcohol after workup: 60%; mp 119–120 °C; IR (Nujol) 1710 cm^{-1}; mass spectrum, m/e 182 (M^+ - CH_2O); ^1H NMR ($CDCl_3$) δ 1.0–2.2 (m, 15 H), 3.3, 3.5 (2 d, J = 12 Hz, 2 H), 4.1 (br s, 2 H).

Determination of pK_a Values. Titration curves were determined at 25 °C with a Radiometer RTS822 automatic titration assembly with the glass electrode precalibrated against four standard buffers. All samples for titration were recrystallized twice and dried before analysis. The required *cis*,*cis*-1,3,5-cyclohexanetricarboxylic acid (**14**) was prepared by hydrogenation of 1,3,5-benzenetricarboxylic acid over Rh/C (5%) in water at 50 psi of H_2 for 40 h. Recrystallization from ethanol–toluene gave **14**, mp 219–220 °C (lit.[11] mp 218–219 °C). An extension of Martin's method[12] was used to obtain pK_a values from the titration curve by using pH values observed after addition of 0.5, 1.0, 1.5, 2.0, and 2.5 equiv of titrant.

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Registry No. 2, 79410-20-1; **2** (trimethyl ester), 79410-21-2; **2**·Na, 79410-22-3; **2**·2Na, 79410-23-4; **2**·3Na, 79410-24-5; **4**, 13987-76-3; **5**, 79420-96-5; **6**, 79410-25-6; **7**, 79410-26-7; **8**, 79410-27-8; **9**, 79410-28-9; **10**, 79410-29-0; **11**, 79410-30-3; **14**, 16526-68-4; **14**·3Na, 79410-31-4; **15**, 79410-32-5; 1,3,5-benzenetricarboxylic acid, 554-95-0.

(10) Peters, J. A.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 1323.

(11) Steitz, A., Jr. *J. Org. Chem.* **1968**, *23*, 2978.

(12) Martin, R. B. *J. Phys. Chem.* **1961**, *65*, 2053. See also: Massey, V.; Alberty, R. A. *Biochem. Biophys. Acta* **1954**, *13*, 354.

Regarding the Mechanism of the Carbonyl-Forming Elimination Reaction of Alkyl Nitrates

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The temperature dependence of k_H/k_D for the formation of benzaldehyde through base-catalyzed HNO_2 elimination from benzyl nitrate is indicative of a tunneling pathway of linear proton transfer. The same criterion applied to the uncatalyzed, gas-phase reaction reveals a cyclic transition state of nonlinear proton transfer. From these and other considerations it has been deduced that the base-catalyzed reaction is best formulated as a cyclic process of linear H transfer and is consistent with an $E_{CO}1cb$ rather than the $E_{CO}2$ mechanism previously claimed.

The base-catalyzed elimination reaction of alkyl nitrates, expressed by eq 1, has been the subject of a considerable

$$RCH_2ONO_2 + Y^- \rightarrow RCH{=}O + NO_2^- + YH \quad (1)$$

number of studies[1-4] which have led to its formulation as a concerted $E_{CO}2$ process. The postulated mechanism has been based on the results of measurements (with benzyl nitrates) of the primary hydrogen–deuterium isotope effects (k_H/k_D) as a function of base, solvent composition, and para substitution, the nitrogen isotope effect (k_{14}/k_{15}) as a function of base strength and para substitution, and occurrence of a minute degree of deuterium exchange in unreacted substrate. In all cases each of the isotope effects were determined at a single temperature in the range of 20–30 °C. Moreover, the reactivity parameters of the uncatalyzed decomposition reaction, which takes place in the absence of solvent according to eq 2, have neither been measured nor taken into consideration.

$$RCH_2ONO_2 \xrightarrow{\Delta} RCH{=}O + HNO_2 \quad (2)$$

The temperature dependence of k_H/k_D constitutes a mechanistic criterion which has been shown to be of particular value in sorting out the structural properties of hydrogen-transfer reaction transition states (TS*).[5-13] This

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