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PAPER

Highly efficient intramolecular Cannizzaro reaction between 1,3-distal formyl groups at the upper rim of a *cone*-calix[4]arene†

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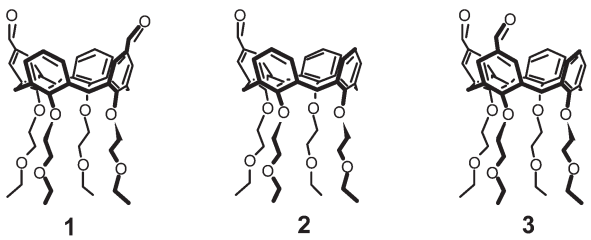
The 1,3-distal *cone*-calix[4]arene dialdehyde **1** undergoes Cannizzaro disproportionation in the presence of strong base, but its 1,2-vicinal regioisomer **3** and the analogous monoaldehyde **2** are unreactive under the same conditions. The high intramolecular reactivity of the 1,3-distal regioisomer **1** is measured and discussed in terms of Effective Molarity (EM).

Either rim of calix[4]arenes has been used for more than two decades as a convenient platform for the introduction of recognition units and catalytic groups.[1] Exhaustive alkylation at the lower rim hydroxyls with groups bulkier than ethyl, strongly reducing the mobility of the calix[4]arene skeleton, prevents the interconversion between *cone*, *partial-cone*, 1,2-*alternate*, and 1,3-*alternate* conformers.[2]

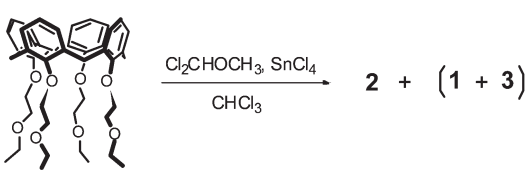
Calix[4]arenes, even when blocked in the *cone* conformation, still retain a certain degree of conformational freedom arising from concerted partial rotations around the CC bonds between the methylene bridges and the aromatic rings. A direct consequence of the residual mobility is the apparent C_{4v} symmetry in the ^{1}H NMR spectra of the tetraalkoxycalix[4]arenes, that results from fast interconversion between two C_{2v} *flattened-cone* conformations.[3] The high flexibility of the *cone*-conformation has been witnessed by the isolation of a number of stable calix[4]arene derivatives in which the 1,3-distal positions of the upper rim are spanned by three-atom COC[4] and SiOSi[5] chains, by two-atom CC[3,6] and NC[7] chains, and even by one methylene group.[8]

Here we report on the highly efficient and selective intramolecular Cannizzaro reaction[9] between the formyl groups of the *cone*-calix[4]arene dialdehyde derivative **1**, as a novel example of 1,3-distal reaction in which a three-atom bridge is formed in the transition state only.



In line with previous reports, Gross formylation of the calix[4]arene derivative **4** with a large excess of $Cl_2CHOCH_3/SnCl_4$ at low temperature (Scheme 1),[10,11] afforded a complex mixture of products with varying formylation degrees. Column chromatography gave the monoformylated derivative **2** in 9% yield, and an unresolved 10 : 1 mixture of 1,3-distal and 1,2-vicinal bisformylated regioisomers **1** and **3**, respectively, in 58% overall yield.

A 0.010 M solution of the (**1** + **3**) mixture in 70% aqueous CH_3OH was refluxed for three days in the presence of 0.20 M NaOH. Column chromatography gave an almost quantitative recovery of unreacted **3**, followed by the disproportionation product **5** in 59% yield, clearly derived from the intramolecular Cannizzaro reaction of **1** (Scheme 2). Structure assignment was based on ^{1}H NMR and mass spectrometric data, and fully confirmed by the X-ray crystal structure shown in Fig. 1. Analogous results were obtained when the (**1** + **3**) mixture (0.010 M) was exposed to the action of 0.20 M CH_3ONa in refluxing



Scheme 1 Gross formylation of compound **4**.

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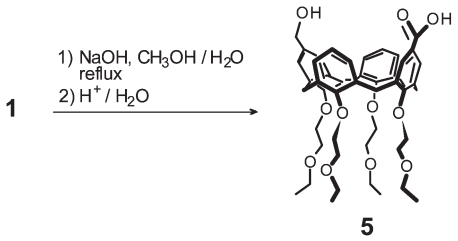
†Electronic supplementary information (ESI) available: Spectroscopic characterization of compounds **5** and **6**, ^{1}H NMR spectrum of the mixture (**1** + **3**). Details of X-ray crystal structure determination. CCDC 836028. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25458a



Scheme 2 Intramolecular Cannizzaro reaction in aqueous methanol.

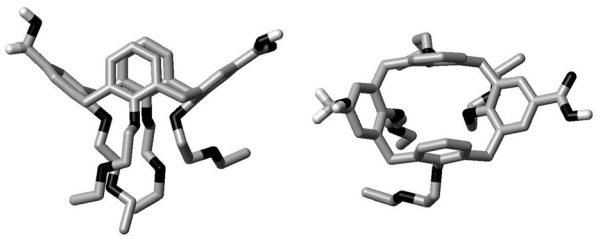
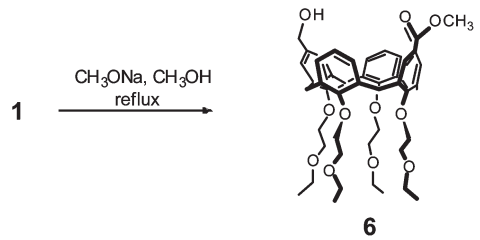


Fig. 1 X-ray diffraction structure of the hydroxyacid **5**. Lateral (left) and apical (right) views. The open *flattened-cone* conformation is dictated by the hydrogen bonding network established in the crystal lattice (see ESI†).



Scheme 3 Intramolecular Cannizzaro reaction in anhydrous methanol.

anhydrous methanol for three days (Scheme 3). The 1,2-vicinal regioisomer **3** was again recovered unchanged, whereas methyl ester **6** was obtained in 60% yield.

Control experiments carried out under identical conditions showed that neither monoaldehyde **2**, nor a pure sample of the 1,2-vicinal dialdehyde **3**, underwent disproportionation to an appreciable extent. These findings strongly argue in favour of the intramolecular character of the Cannizzaro reaction undergone by the 1,3-distal dialdehyde **1**. They also show that the relative positions of the two formyl groups in the 1,2-vicinal regioisomer **3**, unlike those in **1**, are not geometrically suitable for the intramolecular hydride transfer. Fully consistent with the intramolecular nature of the Cannizzaro reaction of **1**, the rate of product formation in 0.20 M CD_3ONa/CD_3OD was found to exhibit a strict first-order dependence in substrate concentration (Fig. 2), with a pseudo-first-order rate constant $k_1 = 1.8 \times 10^{-5}$ s^{-1} at 50 °C. Use of the tetramethylammonium rather than sodium methoxide as base did not affect the rates, showing that the counter-cation effects are not important under the given conditions.

In order to assess the efficiency of an intramolecular reaction in terms of effective molarity (EM),[12,13] a comparison with a

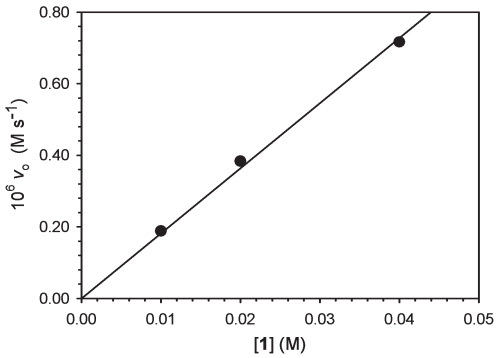
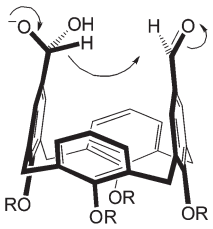


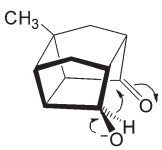
Fig. 2 Cannizzaro reaction of **1** in 0.20 M CD_3ONa in CD_3OD at 50 °C. Initial rate (v_o) of product formation as a function of reactant concentration. The reaction progress was monitored by ^1H NMR, following the aromatic protons adjacent to the carbomethoxy group. The reaction yield was quantitative within the precision of the integrated peak intensities of reactant and product.

suitable intermolecular model reaction is needed. In a careful and extensive investigation of the kinetics of the Cannizzaro reaction of a large number of aromatic aldehydes in 50% aqueous methanol, Tommila[14] reported third-order rate constants, second-order in aldehyde and first-order in base, for benzaldehyde ($k_3 = 2.02 \times 10^{-5}$ M^{-2} s^{-1} at 50 °C) and for *p*-methoxybenzaldehyde ($k_3 = 1.40 \times 10^{-6}$ M^{-2} s^{-1} at 50 °C). The third-order rate constant in anhydrous methanol at 50 °C was also reported for benzaldehyde ($k_3 = 2.21 \times 10^{-6}$ M^{-2} s^{-1}), but not for *p*-methoxybenzaldehyde. Under the assumption that the relative reactivity of benzaldehyde and *p*-methoxybenzaldehyde is the same in 50% methanol and in anhydrous methanol, the quantity $k_3 = 2.21 \times 10^{-6}$ ($1.40 \times 10^{-6}/2.02 \times 10^{-5}$) M^{-2} s^{-1} or 1.5×10^{-7} M^{-2} s^{-1} provides a reasonable estimate of the third-order rate constant of the Cannizzaro reaction of *p*-methoxybenzaldehyde in anhydrous methanol at 50 °C, which translates into a pseudo-second-order rate constant $k_2 = 3.0 \times 10^{-8}$ M^{-1} s^{-1} at 0.20 M base concentration. Taking into account the Cannizzaro reaction of *p*-methoxybenzaldehyde as a reasonable intermolecular model reaction for the intramolecular Cannizzaro reaction of **1**, the ratio $k_1/k_2 = 6 \times 10^2$ M is a measure of the effective molarity EM. A value as high as 6×10^2 M quantifies the high efficiency of the hydride transfer from the anionic tetrahedral function to the neighbouring carbonyl, as schematically depicted in structure **I**. It compares well with the EM values of highly efficient nucleophilic additions to carbonyl involving the formation of 5- and 6-membered rings from conformationally mobile reactants.[12] Yet the EM value for the intramolecular hydride transfer in **I** is four orders of magnitude lower than the EM value of 6.5×10^6 M reported by Davis *et al.*[15] for the analogous reaction of the conjugated base of a rigid hydroxy-ketone structure **II** in 50% aqueous dioxane at 50 °C. The latter is a very remarkable example of an intramolecular reaction, unique of its kind, in which any significant release of strain seems unlikely, and no conformational entropy is obviously lost in the activation process. The agreement between the experimental EM of 6.5×10^6 M or $10^{6.8}$ M and the $10^{6.6}$ M independently estimated by one of us[13] for the maximum entropic advantage of

intramolecular reactions over their intermolecular counterparts, is impressive.



I



II

Unlike **II**, the conformational entropy lost by **I** in the activation process is significant. It requires the complete freezing of the internal rotation around the bonds connecting the two formyl groups to the calix[4]arene backbone, as well around the eight skeletal bonds involving the methylene bridges. If one assumes that the transition state of the Cannizzaro reaction of **1** is strainless, or very nearly so, then the entropic handicap of **I** compared with **II** amounts to about 18 cal K^{-1} mol^{-1}.[16] The entropic cost of freezing the internal rotation of the two formyl groups can be estimated with confidence at 8 to 9 cal K^{-1} mol^{-1},[13,17] corresponding to a rate retarding effect in the range of exp (8/R) or 56 to exp (9/R) or 93. Thus, about half, or slightly less, of the entropic handicap of 18 cal K^{-1} mol^{-1} is accounted for in terms of loss of torsional motions related to the formyl groups. The remaining half, or slightly more, is believed to arise from the loss of skeletal motions occurring when the conformationally mobile *cone* conformation is transformed into the rigid *flattened-cone* conformation (**I**) of the transition state. Under the assumption that the transition state is strainless and conformationally rigid, a value of approximately 9 to 10 cal K^{-1} mol^{-1} provides, to the best of our knowledge, the first estimate of the entropy associated to skeletal motions of a calix[4]arene blocked in the *cone* conformation.

Conclusions

To sum up, the efficiency of the intramolecular hydride transfer occurring in the rate-determining step of the intramolecular Cannizzaro reaction of compound **1** has been measured and discussed in terms of the entropy loss associated with the transformation of the conformationally mobile reactant into a rigid transition state. As a final remark, we point out that the Cannizzaro reaction of compound **1** provides, *inter alia*, an easy route to desymmetrization of 1,3-distal diformylated calix[4]arenes, whose synthetic potential is under current investigation.

Experimental section

Instruments and general methods

^{1}H NMR and ^{13}C NMR spectra were recorded on either a 200 or 300 MHz spectrometer. Chemical shifts are reported as δ values in ppm from tetramethylsilane added as an internal standard. High resolution mass spectra (HRMS) were carried out on an Electrospray Ionisation Time of Flight Micromass spectrometer (HR-ESI TOF). Flash chromatography was performed on Merck silica gel (230–400 mesh).

Materials

CH_3ONa (CD_3ONa) solutions, prepared by addition of sodium metal to CH_3OH (CD_3OD), were titrated with standard hydrochloric acid. Compound **4** was prepared as previously reported.[18]

Kinetics

Kinetic runs were carried out in a NMR tube, in the thermostated probe of the spectrometer. The experiments were run in deuterated methanol at varying concentration of the **1** + **3** mixture (10 : 1, from 0.005 M to 0.04 M **1**) in the presence of 0.20 M CD_3ONa at 50 °C. The reaction progress was monitored by comparison of the ^{1}H NMR singlet of the aromatic protons of the ester **6** adjacent to the carbomethoxy group, and the formyl singlet of the unreactive compound **3** was used as internal standard. Initial rate and time-course based measurements gave the same result within experimental errors for each reaction run.

Compounds 1, 2 and 3

Compound **4** (2 g, 2.83 mmol) was dissolved in dry $CHCl_3$ (60 mL) under an argon atmosphere. The solution was then cooled to −10 °C, and Cl_2CHOCH_3 (9.4 mL, 104 mmol) and $SnCl_4$ (10.7 mL, 90 mmol) were added in the given order. After 40 min following the additions, water (100 mL) was added, and the reaction mixture was allowed to reach room temperature. The mixture was stirred for additional 30 min. The organic phase was separated, washed twice with a Na_2CO_3 saturated solution, once with water, dried, and evaporated to give 1.8 g of crude product as an oil. The crude product was subjected to column chromatography (SiO_2; hexane–ethyl acetate 3 : 1) to give **2** (0.180 g, 9% yield), and a 10 : 1 mixture (1.25 g) of compounds **1** and **3**. Structure assignments were based on comparison of spectral data with those reported in ref. 11.

5-Carboxy-17-hydroxymethyl-25,26,27,28-tetrakis-(2-ethoxyethoxy)calix[4]arene (5)

A 10 : 1 mixture of **1** + **3** (720 mg, 0.94 mmol) was dissolved in methanol (65 mL). To this solution, 28 mL of a 0.67 M NaOH aqueous solution were added. The resulting solution was refluxed for three days. After cooling the reaction mixture was concentrated under vacuum to 4 mL. The strong basic residue was slowly acidified with a 0.1 M HCl solution. This mixture was extracted with CH_2Cl_2 (30 mL) and subsequently the organic phase was washed with water, dried over anhydrous Na_2SO_4, and evaporated to give 550 mg of crude product which was subjected to column chromatography (SiO_2; hexane–ethyl acetate 3 : 2 → ethyl acetate → ethyl acetate–methanol 10 : 1) to give pure **3** as an oil (53 mg, 0.069 mmol, 82% yield), and pure **5** as a white solid (390 mg, 0.50 mmol, 59% yield). Crystals of compounds **5** suitable for X-ray analysis were obtained by slow evaporation from an ethyl acetate solution. Mp 146–148 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.13–1.27 (12H, m), 3.14 (2H, d, J = 13.4 Hz), 3.18 (2H, d, J = 13.4 Hz), 3.44–3.63 (8H, m), 3.73–4.30 (18H, m), 4.47 (2H, d, J = 13.4 Hz), 4.52 (2H, d, J = 13.4 Hz), 5.63 (1H, br s), 6.30 (2H, s), 6.75–6.92 (6H, m), 7.07

(2H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 15.18, 15.26, 30.74, 30.80, 64.16, 66.21, 66.42, 69.54, 69.58, 69.61, 72.71, 73.48, 73.64, 122.55, 122.97, 126.15, 128.57, 128.93, 130.05, 134.06, 134.32, 134.75, 135.24, 135.82, 154.91, 156.97, 160.38, 171.37. UV-Vis (CH_2Cl_2), [λ_{max}/nm (ε/mol^{-1} L cm^{-1})] 259 (9730); 298 (1240). HR-MS calcd for $C_{46}H_{58}O_{11}$ − H^+: 785.3901; found: 785.3921.

5-Carbomethoxy-17-hydroxymethyl-25,26,27,28-tetrakis-(2-ethoxyethoxy)calix[4]arene (6)

The reaction was carried out under an argon atmosphere. A 10 : 1 mixture of **1** + **3** (360 mg, 0.47 mmol) was dissolved in absolute methanol (14 mL). To this solution, 33 mL of a 0.285 M CH_3ONa methanol solution, were added. The resulting mixture was refluxed for 3 days. After cooling the reaction mixture was concentrated under vacuum to 2 mL and water (30 mL) was added to the residue. The water solution was extracted with CH_2Cl_2 (30 mL). The organic phase was washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded 260 mg of crude product which was subjected to column chromatography (SiO_2; hexane–ethyl acetate 3 : 2) to give pure **3** (30 mg, 0.039 mmol, 91% yield, oil) and pure **6** (225 mg, 0.28 mmol, 65% yield, white solid). **6**: Mp 52–55 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.16–1.23 (12H, m), 3.14 (2H, d, J = 13.6 Hz), 3.19 (2H, d, J = 13.6 Hz), 3.48–3.60 (8H, m), 3.78–3.85 (10H, m), 4.05–4.18 (8H, m), 4.25 (3H, s), 4.48 (2H, d, J = 13.6 Hz), 4.53 (2H, d, J = 13.6 Hz), 6.55 (2H, s), 6.58–6.70 (6H, m), 7.28 (2H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 15.21, 15.25, 29.66, 30.77, 30.84, 51.81, 64.70, 66.30, 66.33, 69.60, 69.67, 73.10, 73.21, 73.39, 122.46, 123.57, 126.49, 128.28, 128.55, 129.70, 134.42, 134.75, 134.95, 134.98, 135.38, 155.76, 156.25, 160.72, 167.52. UV-Vis (CH_2Cl_2), [λ_{max}/nm (ε/mol^{-1} L cm^{-1})] 261 (9750); 297 (1260). HR-MS calcd for $C_{47}H_{60}O_{11}$ + Na^+: 823.4033; found: 823.4019.

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