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Trans-1,2-Cyclohexanedicarboxylic Acid Derivatives as pH-Trigger for Conformationally Controlled Crowns

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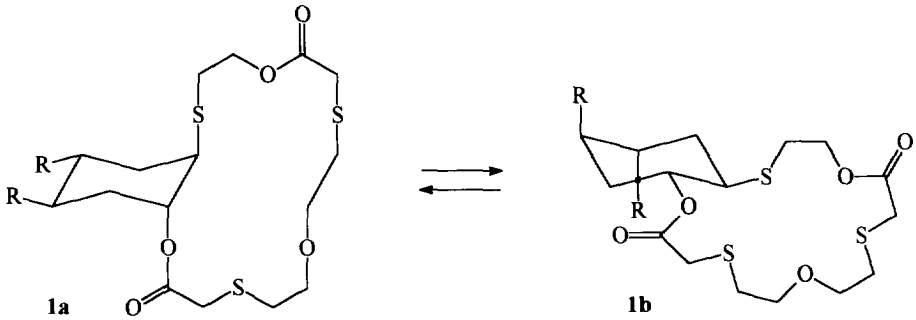
Abstract : *Conversion of trans-1,2-cyclohexanedicarboxylic acid derivatives into dianions under the action of strong bases leads to dramatic conformational changes: a conformer with diaxial position of carboxylate groups becomes predominant. Thus the trans-1,2-cyclohexanedicarboxylic acid moiety can be used for pH-induced conformational switching. The conformational energy changes upon protonation amount to 10 kJ/mol.* Copyright © 1996 Elsevier Science Ltd

Conformational control *via* introduction of various substituent(s) into *trans*-fused six-membered cycle was proposed as a new principle for modification of crown compounds' complexing ability. [1-3] In these structures R plays a role of "conformational lever" and the cyclohexane moiety is a mechanical transmitter. For example, the conformer **1b** is strongly predominant for compounds **1** with R = H (74-88% depending on solvent) and the conformer **1a** dominates when R = COOEt (~90%). [2]

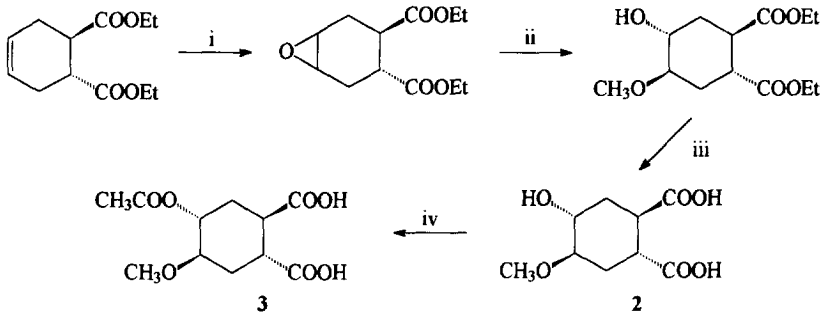


A change of nonbonded interactions between groups R by external influence should change the relative stability of conformers. By affecting this interactions one can control the position of conformational equilibrium of the type **1a** ⇄ **1b**, thus controlling the complexing ability of the macrocycle.

Two carboxylic groups (R = COOH) seem to provide a promising model for this mechanism: their ionization under the action of base should eliminate possible *gauche*-attraction caused by mutual hydrogen bonding and give rise to strong electrostatic *gauche*-repulsion leading to conformational shift **1a** → **1b**. Obviously, protonation of the dianion will return the system to its original position. Conformational changes of this kind were observed for succinic acid and its derivatives. [4,5] Unfortunately, ^{1}H NMR measurements revealed negligible conformational changes in *trans*-1,2-cyclohexanedicarboxylic acid through ionization: both diacid

and its dianion strongly prefer diequatorial conformation (in D_2O solution). [4] The question is then , what type of "trigger" would be needed to bring about the desired conformational changes in structures of type **1**?

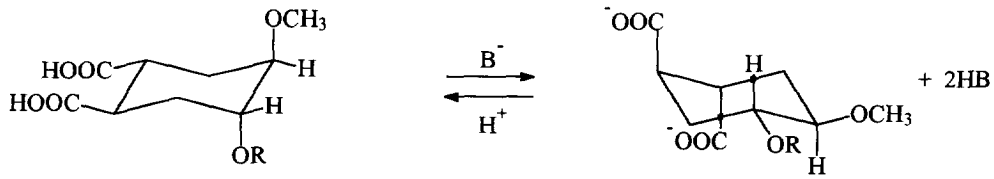
To solve this problem, we synthesized the simple model compounds **2** and **3** as described below:[6]



3 **2**

i, t-BuOOH; ii, CH_3OH/H^+; iii, KOH/H_2O, H^+; iv, $AcCl/Et_2O$;

Free energy differences between conformers ($\Delta G_{2b\text{-}2a,\ 3b\text{-}3a}$) were estimated by ^1H NMR measurements in CD_3OD solutions (Varian VXR-400 ; 400 Mhz) (Table 1) and compared with molecular mechanics calculations (MMX force field).



2a, 3a **2b, 3b**

2, R = H; **3**, R = CH_3CO

The conformer populations (n_a, n_b) were determined using Eliel's equation[7] for H_{OR} signal widths ($W = \Sigma J_{HH}$) measured as a distance between terminal peaks of multiplets: $W = W_a n_a + W_b n_b$.
The signal widths for individual conformers were estimated from measurements with closely related cyclohexane derivatives of completely biased conformational equilibrium [2,3,8]: W_a = 24.5 Hz and W_b = 8.5 Hz for H_{OH}; W_a = 25.5 Hz and W_b = 9.5 Hz for H_{OAc}.

Both **2** and **3** strongly preferred the conformation **a** with equatorial COOH groups. This preference was weaker for compound **2**, probably due to a larger conformational energy of hydroxyl as compared with acetoxy group (4.6 *vs.* 3.3 kJ/mol [9]), and/or an intramolecular hydrogen bond OH···OCH_3 stabilizing the opposite conformer **b**. The predominance of **2a** and **3a** was in accordance with the properties of *trans*-1,2-cyclohexanedicarboxylic acid. [4] MMX calculations (PCMODEL program) also supported these data resulting in $\Delta E_{3b\text{-}3a}$ = 11.4 kJ/mol (energy difference between conformers with optimal rotational positions of all attached groups). It is interesting to note that molecular mechanics did not reveal any hydrogen bonding between vicinal COOH groups (related findings were reported earlier [4]).

Table 1 ^{1}**H NMR data and conformational parameters**

Compound and base	δH_{OR}, p.p.m.	$W(J+J+J)$ [a], H z	n_a, %	ΔG_{b-a}, kJ/mol
2	3.87	10.4 (3.5 + 3.5+ 3.5)	88	5.0
2 + Et_4NOH [b]	3.75	22.6 (10.2 + 8.1 + 4.4)	12	-5.0
3	4.83	9.5 (3.2 + 3.2 + 3.2)	~100	>8
3 + Py [c]	5.21	9.5 (3.2 + 3.2 + 3.2)	~100	>8
3 + Et_3N [d]	4.97	14.1 (5.2 + 5.2 + 3.8)	71	2.2
3 + Et_4NOH [b]	5.14	20.8 (8.7 + 7.8 + 4.3)	29	-2.2

a) direct measurement; b) large excess of base; c) solution in d_6-pyridine; all other measurements in CD_3OD; d) 1:3.

In order to change the interaction between the carboxylic groups *via* their ionization, we added excess of bases: pyridine, triethylamine and tetraethylammonium hydroxide (see Table 1). One can expect Py (pK_{PyH^+} 4.6) to ionize only one carboxyl group in view of the difference in the $pK_a(1)$ and $pK_a(2)$ values for vicinal diacids (for succinic acid $pK_a(1)$ 4.2, $pK_a(2)$ 5.6). This should lead to a stronger electrostatic *gauche*-attraction thus fixing conformer **a**. Indeed, for solution of **3** in d_5-Py we obtained the same spin-spin coupling constants as for the solution in CD_3OD, indicating a complete predominance of the **3a** form. Addition of Et_3N ($pK_{Et_3NH^+}$ 10.75) to methanolic solution shifted the equilibrium towards **3b** significantly. Addition of Et_4NOH made the conformer **3b** to dominate (~70%). Under the same conditions the population of **2b** approached **90%**. To the best of our knowledge this is the largest conformational change ever achieved through deprotonation-protonation of *vic*-dicarboxylic acids (see refs. 4,5, and and refs. therein). The conformational free energy differences caused by protonation / deprotonation amounts to 10 kJ/mol for **2**, and to ≥10 kJ/mol for **3** (see table 1), thus providing a powerful pH trigger. . The observed difference of 10 kJ/mol agrees well with the known differences between free energies of the conformational equilibrium **1a** ⇌ **1b** for R = H and R = COOEt (-4.9 and 5.2 kJ/mol, respectively, in d_6-acetone).[2]

Thus the *trans*-1,2-cyclohexanedicarboxylic acid moiety can be used for pH-induced conformational switching capable to change the preferred conformation of various complexing agents (*e.g.* of the type **1**), thereby modifying their complexing ability[10]. The strong conformational coupling between two different binding sites in compounds like **3** should allow the development of new heterotopic allosteric systems with high positive or negative cooperativity.

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REFERENCES AND NOTES

1. (a) Samoshin, V.V.; Zelenkina, O.A.; Yartseva, I.V.; Zefirov, N.S. *Zh.Org.Khim.*, **1987**, *23*, 2244-2245.
(b) Samoshin, V.V.; Zelenkina, O.A.; Subbotin, O.A..; Sergeev, N.M.; Zefirov, N.S. *Zh.Org.Khim.*, **1988**, *24*, 465-470.
(c) Samoshin, V.V.; Yartseva, I.V.; Zelenkina, O.A.; Zefirov, N.S. *Zh.Org.Khim.*, **1988**, *24*, 2455-2456.
(d) Samoshin, V.V.; Zelenkina, O.A.; Yartseva, I.V.; Subbotin, O.A.; Zefirov, N.S. *Zh.Org.Khim.*, **1988**, *24*, 2458-2459.
2. Samoshin, V.V.; Vereshchagina, Ya.A.; Konoplyanko, N.V.; Lutsenko, A.I.; Zefirov, N.S. *Zh.Org.Khim.*, **1993**, *29*, 213-215.
3. Samoshin, V.V.; Vereshchagina, Ya.A.; Lutsenko, A.I.; Zefirov, N.S. *Zh.Org.Khim.*, **1993**, *29*, 1095-1100.
4. Abraham, R.J.; Hudson, B.D.; Thomas, W.A. *J.Chem.Soc., Perkin Trans. II*, **1986**, 1635-1640.
5. (a) Nunes, M.T.; Gil, V.M.S.; Ascenco, J. *Tetrahedron*, **1981**, *37*, 611;
(b) Marawetz, H.; Choi, L.-S. *J.Phys.Chem.*, **1986**, *90*, 4119.
6. *cis-4-Hydroxy-trans-5-methoxy-trans-1,2-cyclohexanedicarboxylic acid* (**2**) :
yield 78%; m.p 160°C (Et_2O-MeOH, 10:1); ^1H NMR (CD_3OD) : 1.85 (m, 3H); 2.03 (dt, 1H, J = 13.9, 3.8, 3.8 Hz); 2.81 (ddd, 1H, J = 11.6, 11.0, 3.7); 2.94 (ddd, 1H, J = 11.1, 11.1, 4.2); 3.33 (q, 1H, J = 3.4); 3.38 (s, 3H); 3.87 (q, 1H, J = 3.5).

   cis-4-Acetoxy-trans-5-methoxy-trans-1,2-cyclohexanedicarboxylic acid (**3**) :
yield 51%; m.p 178°C (Et_2O-MeOH, 10:1); ^1H NMR (CD_3OD) : 1.55 (ddd, 1H, J = 14.1, 12.5, 2.5); 1.73 (ddd, 1H, J = 14.9, 12.2, 2.9); 1.84 (ddd, 1H, J = 14.4, 3.5, 3.5); 1.89 (s, 3H); 1.97 (ddd, 1H, 13.8, 3.1, 3.1); 2.65 (ddd, 1H, 10.7, 10.7, 4.0); 2.70 (ddd, 1H, 10.8, 10.8, 3.7); 3.19 (s, 3H); 3.24 (q, 1H, J = 3.3); 4.83 (q, 1H, J = 3.2).
7. Eliel, E.L. *Chemistry and Industry* **1959**, 568.
8. Samoshin, V.V.; Zapolsky, M.E.; Yartseva, I.V.; Zefirov, N.S. *Zh.Org.Khim.*, **1988**, *24*, 2455-2456.
9. Schneider, H.-J.; Hoppen, V. *J.Org.Chem.*, **1978**, *43*, 3866-3873.
10. For a related system with pH dependent conformational coupling to heterotopic binding sites see Schneider, H.-J.; Güttes, D.; Schneider, U. *J.Am.Chem.Soc.* **1988**, *110*, 6449-6454, and references cited therein.

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