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trans-2-Aminocyclohexanols as pH-triggers for conformationally controlled crowns and podands☆

Vyacheslav V. Samoshin,[a,*] Vyacheslav A. Chertkov,[b] Dmitriy E. Gremyachinskiy,[a] Elena K. Dobretsova,[a] Alla K. Shestakova[c] and Lidia P. Vatlina[d]

[a]*Lomonosov Moscow State Academy of Fine Chemical Technology, Vernadsky Prospect 86, Moscow 117571, Russia*
[b]*Lomonosov Moscow State University, Department of Chemistry, Moscow 119899, Russia*
[c]*State Research Institute of Chemistry and Technology of Organoelement Compounds, Moscow 111123, Russia*
[d]*Ushinsky Yaroslavl State Pedagogic University, Yaroslavl 150000, Russia*

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Abstract—Protonation of *trans*-2-aminocyclohexanols leads to dramatic conformational changes: due to an intramolecular hydrogen bond a conformer with equatorial position of ammonio- and hydroxy-groups becomes predominant. The *trans*-2-aminocyclohexanol moiety has been used for pH-induced conformational switching of a crown ether and a podand.
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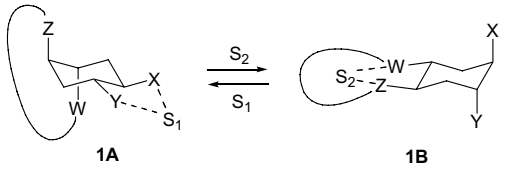
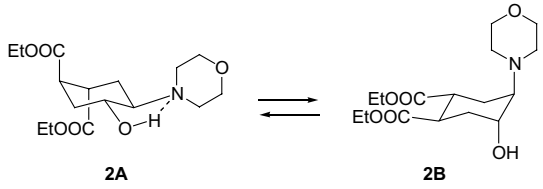
Conformational control via introduction of various substituent(s) into *trans*-fused six-membered cycle was proposed by us as a new principle for modification of the complexing ability of (cyclohexano)crown compounds and non-cyclic ionophores (podands).[1–20] In these structures, a substituent plays a role of 'conformational lever', and the cyclohexane moiety is a mechanical transmitter. The cyclohexane mechanism can also imitate allosteric effect by transmitting a conformational change from one binding site (macroheterocycle or podand) to another (Scheme 1).[1,9,10,14,17–20] These ideas were later successfully explored also by other researchers,[21–25] and were expanded to decaline and perhydroanthracene derivatives.[26–30]



Scheme 1.

A change of non-bonded interactions between groups X and Y (and/or W and Z) by external influence, for example, by interaction with a guest S, should change the relative stability of conformers. By affecting these interactions one can control the position of conformational equilibrium of the type **1A** ⇄ **1B**, thus controlling the complexing ability of the macrocycle or podand. Two carboxylic groups (X = Y = COOH) provide a promising model for this mechanism.[17] Their ionization under the action of base eliminates possible *gauche*-attraction caused by mutual hydrogen bonding and gives rise to a strong electrostatic *gauche*-repulsion leading to conformational shift **1A** → **1B**. Protonation of the dianion returns the system to its original position. The power of such a conformational trigger was estimated experimentally as ⩾10 kJ/mol.[17]

Another promising type of a conformational pH-trigger is provided by *trans*-2-aminocyclohexanol moiety. We found previously[18] that compound **2** adopted



Scheme 2.

Keywords: *trans*-2-Aminocyclohexanol; pH-switch; Cyclohexano crown ether; Conformations.

☆ See Ref. 1.

* Corresponding author at present address: Department of Chemistry, University of the Pacific, Stockton, CA 95211, USA. Tel.: +1 209 946 2921; fax: +1 209 946 2607; e-mail: vsamoshin@pacific.edu

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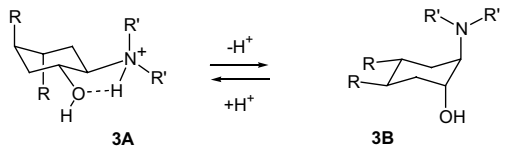
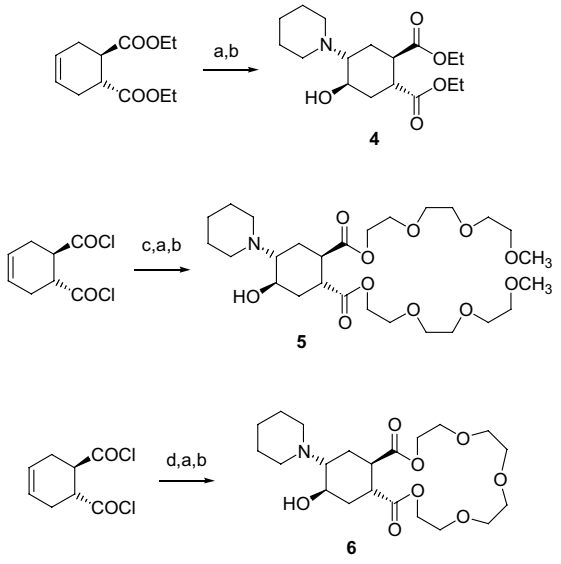


Scheme 3.



Scheme 4. Synthesis of compounds **4**–**6**: (a) *m*-$ClC_6H_4CO_3H$, rt; (b) piperidine/H_2O/*i*-PrOH, rt, 56%, 44% and 54% for **4**, **5** and **6**, respectively; (c) $Me(OCH_2CH_2O)_3OH$, Py, reflux in PhMe, 63%; (d) tetraethyleneglycol, Py, reflux in PhMe, 38%.[12,13]

predominantly the conformation **2A** in $CDCl_3$, but the conformation **2B** in methanol or DMSO (Scheme 2).

This dramatic change, which exceeded 10 kJ/mol in terms of the relative conformational stability, was attributed to destruction of the stabilizing intramolecular hydrogen bond OH···N in **2A** by the solvents—hydrogen bond acceptors.[18] Another way to control such a conformational equilibrium would be an addition of acid to protonate the amino group, and to generate the possibly stronger intramolecular hydrogen bond of HO···H–N^+ type (Scheme 3). This bond would stabilize conformation **3A**, thus moving the groups R away from each other, and decreasing their ability to interact with another molecule or ion, for example, to form complexes like **1B**. The hydrogen bonds of both types are known to convert a chair ring into a twist conformation in aminohydroxy steroids.[31,32]

To explore this option, we synthesized compounds **4**–**6** (Scheme 4), and evaluated their conformational behaviour in various conditions.

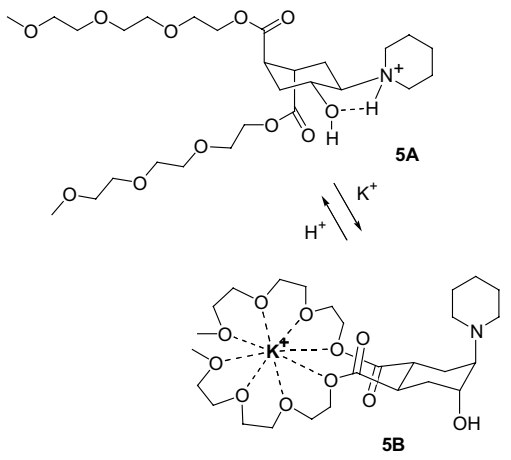
Free energy differences between conformers (ΔG_{B-A}) were estimated by ^{1}H NMR measurements in CD_3OD solutions (Varian VXR-400; 400 MHz) (Table 1). The conformer populations (n_A, n_B) were determined using Eliel's equation[33] for signal widths ($W = \sum J_{HH}$) of the cyclohexane protons H_1, H_2, H_4 and H_5, measured as a distance between terminal peaks of a multiplet: $W_{observed} = W_A n_A + W_B n_B$. The signal widths for individual conformers were estimated from measurements for compounds **4**–**6** and for closely related cyclohexane derivatives with completely biased conformational equilibrium:[14–18] $W_A = 25.7$ Hz and $W_B = 9$ Hz for H_{OH}, $W_A = 26.6$ Hz and $W_B = 10$ Hz for $H_{NR'2}$, and $W_A = 9$ Hz and $W_B = 30$ Hz for H_{COOR}. The most accurate estimations were obtained from the data for H_{OH} signal.

The conformation A is somewhat preferred for compounds **4** and **5**. Unexpectedly, **5A** is more predominant than **4A**. This difference may be attributed to the stronger electrostatic attraction between COOR groups in **4** (smaller ester groups can find a better rotational position for interaction), and/or to the stronger steric repulsion between COOR groups in **5**, which is increased by solvation of polyether chains R with methanol molecules. On contrary, the crown ether **6** prefers the conformation **6B** with both ester groups equatorial. This is apparently yet another manifestation of the 'contraction effect' of macrocycle.[2–5,7,11,13–16,19]

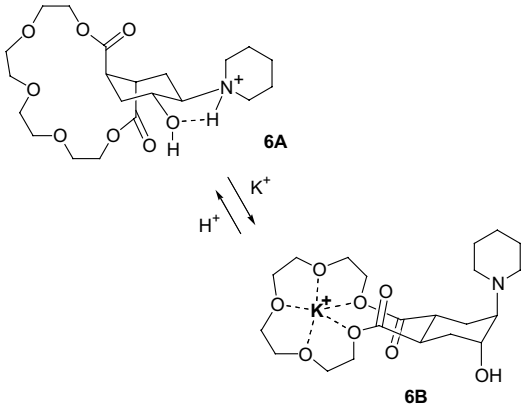
Table 1. ^{1}H NMR data and conformational parameters

Compound and additives[a]	H_{OH}		H_N		$H_{COOR\,(1)}$		$H_{COOR\,(2)}$		n_A, %	ΔG_{B-A}, kJ/mol
	δ	W, Hz	δ	W, Hz	δ	W, Hz	δ	W, Hz		
4	3.81	18.4	2.22	18.7	3.12	17.7	3.05	17.2	56	0.6
4 + AcOH	3.85	25.5	3.11	26.4	3.36	~12[b]	3.3	[b]	~100	>9
4 + KI	3.82	18.5	2.23	18.6	3.12	17.5	3.07	17.1	56	0.6
5	3.78	20.1	2.29	20.5	3.21	~17[b]	3.16	~17[b]	65	1.5
5 + AcOH	3.89	25.7	3.12	26.6	3.4	[b]	3.4	[b]	~100	>9
5 + KI	3.92	17.1	2.3	[c]	3.19	~19[b]	3.13	[b]	49	−0.1
5 + KI + AcOH	3.95	25.7	3.20	26.6	3.4	[b]	3.4	[b]	~100	>9
6	3.95	14.7	2.21	14.6	3.13	22.1	3.02	21.2	35	−1.5
6 + AcOH	4.01	25.4	3.20	~25[c]	3.4	[b]	3.4	[b]	~100	>9
6 + KI	4.12	12	2.27	[c]	3.2	[b]	3.2	[b]	20	−3.5
6 + KI + AcOH	4.01	25.1	3.22	26	3.45	11	3.40	11	95	7.5

[a] In CD_3OD solution; AcOH and/or KI were added in large excess.
[b] Partially or completely overlapped with other signals.
[c] Poorly resolved multiplet.



Scheme 5.



Scheme 6.

As expected, all the studied structures demonstrate a dramatic switch to A conformation with excess acid (Table 1; Schemes 5 and 6). The power of this conformational trigger can be estimated from the measurements for compound **6** as $\geqslant$10.5 kJ/mol. Moreover, the acid-induced twisting of six-membered cycle in aminohydroxy steroids[31,32] proves that the actual power of such triggers may be well above 20 kJ/mol.

Possessing two different binding sites, these compounds are interesting models for a negative allosteric effect. Presumably, the macrocycle in **6** and polyether chains in **5** should be able to form complexes with metal cations. Only conformations **5B** and **6B** provide the necessary geometrical arrangement for such complexation. Indeed, the conformational equilibria were shifted to these conformations when the methanolic solutions of **5** or **6** were saturated with KI (Table 1; Schemes 5 and 6). This effect was not strong—approximately 1.5–2 kJ/mol. Addition of excess acetic acid to these solutions completely switched the equilibrium to alternative conformations **5A** and **6A**. The conformational equilibrium for compound **4** was reasonably indifferent to the addition of potassium salt.

Thus the *trans*-2-aminocyclohexanol moiety can be used for pH-induced conformational switching capable to change the preferred conformation of various complexing agents thereby modifying their complexing ability. The strong conformational coupling of two different binding sites in compounds like **5** or **6** should allow the development of new heterotopic allosteric systems with high negative cooperativity, which may be especially useful for a selective membrane transport.

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References and notes

1. Partially reported at *International Minisymposium* '*Modern Trends in Organic Chemistry—New Materials and Reaction Design*', Universität des Saarlandes, Saarbrücken, Germany, 1997.
2. Samoshin, V. V.; Subbotin, O. A.; Zelenkina, O. A.; Zefirov, N. S. *Zh. Org. Khim.* **1986**, *22*, 2231–2232 (*Russ. J. Org. Chem.* **1986**, *22*, 2004–2005).
3. Samoshin, V. V.; Zelenkina, O. A.; Subbotin, O. A.; Zefirov, N. S. *Zh. Org. Khim.* **1987**, *23*, 1319–1320 (*Russ. J. Org. Chem.* **1987**, *22*, 1192–1193).
4. Samoshin, V. V.; Zelenkina, O. A.; Yartseva, I. V.; Zefirov, N. S. *Zh. Org. Khim.* **1987**, *23*, 2244–2245 (*Russ. J. Org. Chem.* **1987**, *23*, 1984–1985).
5. Samoshin, V. V.; Zelenkina, O. A.; Subbotin, O. A.; Sergeev, N. M.; Zefirov, N. S. *Zh. Org. Khim.* **1988**, *24*, 465–471 (*Russ. J. Org. Chem.* **1988**, *24*, 413–418).
6. Samoshin, V. V.; Yartseva, I. V.; Zelenkina, O. A.; Zefirov, N. S. *Zh. Org. Khim.* **1988**, *24*, 2455–2456 (*Russ. J. Org. Chem.* **1988**, *24*, 2215–2216).
7. Samoshin, V. V.; Zelenkina, O. A.; Yartseva, I. V.; Subbotin, O. A.; Zefirov, N. S. *Zh. Org. Khim.* **1988**, *24*, 2458–2459 (*Russ. J. Org. Chem.* **1988**, *24*, 2217–2218).
8. Samoshin, V. V.; Zapol'skiy, M. E.; Lutsenko, A. I.; Zelenkina, O. A.; Zefirov, N. S. *Zh. Org. Khim.* **1989**, *25*, 651–652 (*Russ. J. Org. Chem.* **1989**, *25*, 586–587).
9. Samoshin, V. V.; Zelenkina, O. A.; Zapol'skiy, M. E.; Vereshchagina, Ya. A.; Zefirov, N. S. *Abstracts of 15th International Symposium on Macrocyclic Chemistry*, Odessa, USSR, 1990; 182.
10. Samoshin, V. V.; Zefirov, N. S. *Abstracts of 16th International Symposium on Macrocyclic Chemistry*, Sheffield, UK, 1990; ST30.
11. Tsingarelli, R. D.; Shpigun, L. K.; Samoshin, V. V.; Zelyonkina, O. A.; Zapolsky, M. E.; Zefirov, N. S.; Zolotov, Yu. A. *Analyst* **1992**, *117*, 853–856.
12. Potekhin, K. A.; Struchkov, Yu. T.; Konoplyanko, N. V.; Samoshin, V. V.; Zefirov, N. S. *Dokl. Akad. Nauk* **1992**, *326*, 1007–1009.
13. Samoshin, V. V.; Konoplyanko, N. V.; Lutsenko, A. I.; Zefirov, N. S. *Zh. Org. Khim.* **1992**, *28*, 867–869 (*Russ. J. Org. Chem.* **1992**, *28*, 668–669).
14. Samoshin, V. V.; Vereshchagina, Ya. A.; Konoplyanko, N. V.; Lutsenko, A. I.; Zefirov, N. S. *Zh. Org. Khim.* **1993**, *29*, 213–215 (*Russ. J. Org. Chem.* **1993**, *29*, 183–184).
15. Samoshin, V. V.; Vereshchagina, Ya. A.; Lutsenko, A. I.; Zefirov, N. S. *Zh. Org. Khim.* **1993**, *29*, 1095–1100 (*Russ. J. Org. Chem.* **1993**, *29*, 910–914).

16. Troyansky, E. I.; Ismagilov, R. F.; Samoshin, V. V.; Strelenko, Yu. A.; Demchuk, D. V.; Nikishin, G. I.; Lindeman, S. V.; Khrustalev, V. N.; Struchkov, Yu. T. *Tetrahedron* **1995**, *51*, 11431–11444.
17. Samoshin, V. V.; Chertkov, V. A.; Vatlina, L. P.; Dobretsova, E. K.; Simonov, N. A.; Kastorsky, L. P.; Gremyachinsky, D. E.; Schneider, H.-J. *Tetrahedron Lett.* **1996**, *37*, 3981–3984.
18. Samoshin, V. V.; Bychkova, O. V.; Chertkov, V. A.; Shestakova, A. K.; Vatlina, L. P.; Simonov, N. A.; Kastorsky, L. P. *Zh. Org. Khim.* **1996**, *32*, 1104–1105 (*Russ. J. Org. Chem.* **1996**, *32*, 1066–1067).
19. Samoshin, V. V.; Troyansky, E. I. *Phosphorus, Sulfur, Silicon* **1997**, *120/121*, 181–196.
20. Samoshin, V. V.; Troyansky, E. I. Conformations of crown thioethers. *Abstracts of 213th National Meeting of the American Chemical Society*, San Francisco, USA, 1997; ORGN 354.
21. Raban, M.; Quin, J.; Belguise, A. *Tetrahedron Lett.* **1991**, *32*, 35–38.
22. Raban, M.; Burch, D. L.; Hortelano, E. R.; Durocher, D. *J. Org. Chem.* **1994**, *59*, 1283–1287.
23. Costero, A. M.; Rodriguez, S. *Tetrahedron Lett.* **1992**, *33*, 623–626.
24. Costero, A. M.; Rodriguez, S. *Tetrahedron* **1992**, *48*, 6265–6272.
25. Costero, A. M.; Villarroya, J. P.; Gil, S.; Aurell, M. J.; de Arellano, M. C. R. *Tetrahedron* **2002**, *58*, 6729–6734.
26. Berninger, J.; Krauss, R.; Weining, H.-G.; Koert, U.; Ziemer, B.; Harms, K. *Eur. J. Org. Chem.* **1999**, 875–884.
27. Krauss, R.; Weining, H.-G.; Seydack, M.; Bendig, J.; Koert, U. *Angew. Chem., Int. Ed.* **2000**, *39*, 1835–1837.
28. Koert, U.; Krauss, R.; Weining, H.-G.; Heumann, C.; Ziemer, B.; Mügge, C.; Seydack, M.; Bendig, J. *Eur. J. Org. Chem.* **2001**, 575–586.
29. Weining, H.-G.; Krauss, R.; Seydack, M.; Bendig, J.; Koert, U. *Chem. Eur. J.* **2001**, *7*, 2075–2088.
30. Karle, M.; Bockelmann, D.; Schumann, D.; Griesinger, C.; Koert, U. *Angew. Chem., Int. Ed.* **2003**, *42*, 4546–4549.
31. Schneider, H.-J.; Buchheit, U.; Gschwendtner, W.; Lonsdorfer, M. Steric Distortions and Polar Effects in Steroids: Molecular Mechanics Calculations and ^{13}C NMR Investigations. In *Molecular Structure and Biological Activity*; Griffin, J. F., Duax, W. L., Eds.; Elsevier: New York, 1982; p 165.
32. Kooijman, H.; Kelder, J.; Kanters, J. A.; Duisenberg, A. J. M.; Kroon, J. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2133–2140.
33. Eliel, E. L. *Chem. Ind.* **1959**, 568.