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). 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). These ideas were later successfully explored also by other researchers, and were expanded to decaline and perhydroanthracene derivatives.

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 $1A \rightleftharpoons 1B$, thus controlling the complexing ability of the macrocycle or podand. Two carboxylic groups (X = Y = COOH) provide a promising model for this mechanism. 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 $1A \rightarrow 1B$. Protonation of the dianion returns the system to its original position. The power of such a conformational trigger was estimated experimentally as $\geq 10$kJ/mol.

Another promising type of a conformational pH-trigger is provided by trans-2-aminocyclohexanol moiety. We found previously that compound 2 adopted
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 from 1H NMR measurements in CD3OD solutions (Varian VXR-400; 400 MHz) (Table 1). The conformer populations (n_B, n_A) were determined using Eliel’s equation 33 for signal widths (W = \sum A_{HH}) of the cyclohexane protons H1, H2, H4 and H5, 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 HOH, W_A = 26.6 Hz and W_B = 10 Hz for HNR, and W_A = 9 Hz and W_B = 30 Hz for HCOOR. The most accurate estimations were obtained from the data for HOH 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 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 macrocycles. 2,5-7,11,13-16,19

### Table 1. 1H NMR data and conformational parameters

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<th>Compound and additives</th>
<th>HOH δ</th>
<th>HOH W, Hz</th>
<th>HN δ</th>
<th>HN W, Hz</th>
<th>HCOOR (1) δ</th>
<th>HCOOR (1) W, Hz</th>
<th>HCOOR (2) δ</th>
<th>HCOOR (2) W, Hz</th>
<th>n_A, %</th>
<th>ΔG_B-A, kJ/mol</th>
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*a* In CD3OD solution; AcOH and/or KI were added in large excess.

*Partial or completely overlapped with other signals.

*Poorly resolved multiplet.*
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.

Acknowledgements

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References and notes


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 $\geq 10.5$ kJ/mol. Moreover, the acid-induced twisting of six-membered cycle in aminohydrino trigger can be estimated from the measurements (Table 1; Schemes 5 and 6). The power of this conformational switch to A conformation with excess acid 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 $\geq 10.5$ kJ/mol. Moreover, the acid-induced twisting of six-membered cycle in aminohydrino trigger can be estimated from the measurements (Table 1; Schemes 5 and 6). The power of this conformational switch to A conformation with excess acid

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