Cyclohexane-Based Conformationally Controlled Crowns and Podands

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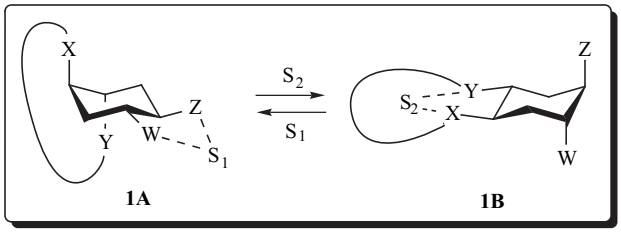
Abstract: Cyclohexane-based conformationally controlled ionophores, the emerging new class of molecular switches, provide a new and promising approach to allosteric systems with negative cooperativity.

Keywords: Molecular switches, cyclohexano crown-ethers, conformational transmitters.

Dedicated to Academician Nikolai S. Zefirov on Occasion of his 70th Birthday

INTRODUCTION

Molecular switches are molecules that can reversibly change their states and properties under external influence [1-3]. Allosteric switches are host compounds containing at least two spatially separated binding sites that are conformationally coupled. When one site is occupied, it changes conformation, and this 'signal', mechanically transmitted by the structure of the molecule, induces a conformational change in the second site, thus increasing (positive cooperativity) or decreasing (negative cooperativity) its affinity to an appropriate guest. Negative cooperativity has been less explored than the positive, though it may be more interesting for applications, such as membrane transport, drug delivery, catalysis, etc. [1-3]. Cyclohexane-based conformationally controlled ionophores provide a new and promising approach to allosteric systems with negative cooperativity.



Conformational control *via* introduction of various substituent(s) into a *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-macrocyclic ionophores (podands) [4-21]. Similar idea was suggested for cyclohexane-based podands by Raban *et al.* [22-25]. In these structures, a substituent plays a role of 'conformational lever', and the cyclohexane moiety is a mechanical transmitter. The cyclohexane machinery can also mimic an allosteric effect by transmitting a conformational change (signal) from one complexing center (macroheterocycle or podand) to another, which results in controllable conformational equilibrium of the type **1A** $\rightleftarrows$ **1B** [14,17-19]. These ideas were successfully explored also by Costero *et al.* [26-30], and were expanded by Koert *et al.* [31-36] to decaline and perhydroanthracene derivatives.

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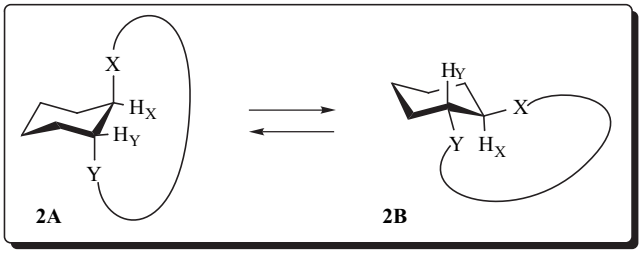
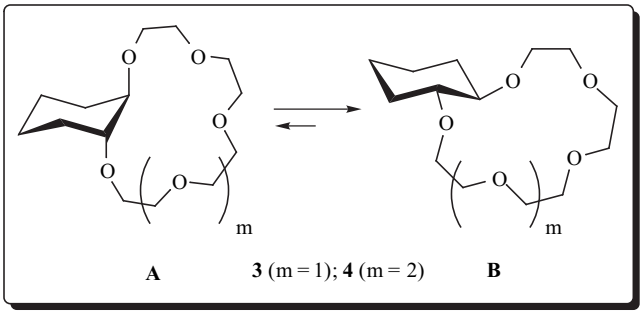
CONFORMATIONS OF CYCLOHEXANO CROWN COMPOUNDS

A complete conformational analysis for crown compounds is an extremely difficult task due to the enormous number of possible conformers (for example, see [37]). Relatively rigid structural fragments may simplify the analysis [37]. In particular, an introduction of a *trans*-fused cyclohexane moiety restricts movement of one O-C-C-O (in general, X-C-C-Y) fragment to only two possible conformations – *gauche* and *anti* – thus restraining the conformational flexibility of the macrocycle. Moreover, the six-membered cycle in these molecules provides a 'probe' for conformational studies. The well developed methods of conformational measurements for cyclohexane derivatives, especially ^{1}H and ^{13}C NMR techniques, can be applied to determination of the free energy difference, $\Delta G_{\mathbf{B-A}}$, between the conformer **2B** with a ring-shaped macrocycle and the conformer **2A** with a 'stretched', or 'oval' form of the crown cycle.



Although the major part of the macrocycle beyond the bridge fragment XCCY is not characterized by the conformational parameters of the cyclohexane moiety, this approach allows obtaining important information (Table **1**).



As could be expected, the conformer **B** with equatorial orientation of C-O bonds is predominant for both *trans*-cyclohexano-15-crown-5 (**3**) [9] and *trans*-cyclohexano-18-

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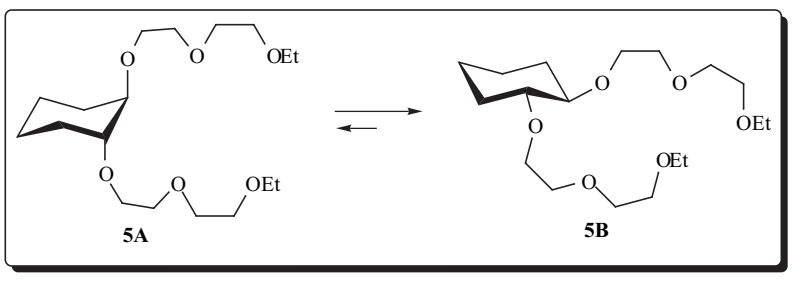
Table 1. Conformational Parameters of *trans*-Cyclohexanocrown (Thiacrown) Ethers and Podands

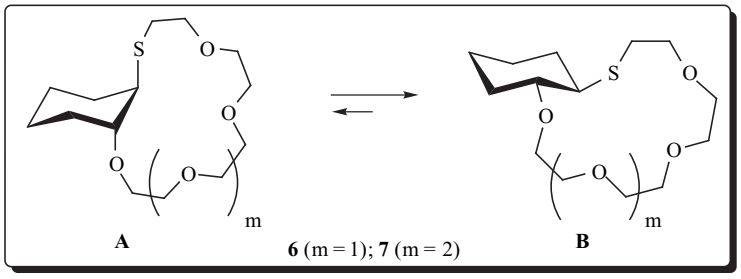
Compound	Conditions	n_A, %	ΔG_{B-A}, kJ/mol	Refs.
3	CS_2 (-69°C) [a]	9.1	-3.9	[9]
4	CS_2 (-79°C) [a] CD_2Cl_2 (-77°C) [a] CD_3OD (-85°C) [a]	4.5 <2 <2	-4.9 <-6.2 <-6.2	[4]
5	CS_2 (-85°C) [a]	12	-3.1	[5]
6	C_6D_{12} [b] $(CD_3)_2CO$ [b]	40 32	-1.0 -1.9	[10]
7	C_6D_{12} [b] $(CD_3)_2CO$ [b]	31 20	-2.0 -3.4	[10]
8	CD_3OD [b]	68	1.9	[6]
9	C_6D_{12} [b] $(CD_3)_2CO$ [b]	89 75	5.1 2.8	[9]
10	C_6D_{12} [b] $(CD_3)_2CO$ [b]	85 67	4.2 1.8	[9]
11	C_6D_{12} [b] CD_3CN [b]	16 14	-4.2 -4.6	[15,19]
12	C_6D_{12} [b] CD_3CN [b]	12 4	-5.1 -7.9	[15,19]
13	C_6D_{12} [b] CD_3CN [b]	89 74	5.2 2.6	[15,19]
14	(-90°C) [c]	91 [d]	3.5 [d]	[22]
15	(-90°C) [c]	>98 [e]	>6 [e]	[22]
17	CD_2Cl_2 (-90°C) [c] CD_3OD (-90°C) [c]	93 f 95 [g]	3.8 4.6	[25]
18	C_6D_{12} [b] $(CD_3)_2CO$ [b]	26 12	-2.6 -4.9	[14,19]
19	C_6D_{12} [b] $(CD_3)_2CO$ [b]	87 89	4.8 5.2	[14,19]
30	CD_3OD [b]	65	1.5	[20,21]
31	CD_3OD [b]	35	-1.5	[20,21]

a) Integration in the low-temperature ^{13}C NMR; b) Measurement of the conformationally averaged couplings (signal widths) in the room-temperature ^1H NMR; c) Integration in the low-temperature ^1H NMR; d) $K_{eq} = 0.1$ [22]; e) $K_{eq} < 0.02$ [22]; f) $K_{eq} = 0.08$ [25]; g) $K_{eq} = 0.05$ [25].

crown-6 (**4**) [4]. The predominance increases with the solvent polarity. The equilibria are more biased than the one for the podand (**5**) [5], which in turn has a higher population of the diequatorial conformer **B** than *trans*-1,2-dimethoxycyclohexane [38].

This conformational shift was described as a 'contraction effect' of the macrocycle [4-7,9,11,13-16,19-21]. Its magnitude was measured as a deviation of the free energy difference for the **A** ⇄ **B** equilibrium (ΔG_{B-A}; see Table **1**) from the analogous parameter for *trans*-1,2-dimethoxycyclohexane, and was estimated as 2.7 kJ/mol for





3 [9] and 3.7 kJ/mol for **4** [4]. Quite counter-intuitively, the contraction effect is stronger in **4** compared to **3**. In other words, the larger 18-membered macrocycle is more difficult to stretch to an 'oval' shape **2A** than the smaller 15-membered one (by 1 kJ/mol).[1] The same trend was found for substituted 15- and 18-membered *trans*-cyclohexano crown ethers **9** and **10** (see the next section) [9].

In the case of the *trans*-cyclohexano monothiacrown ethers **6** and **7**, the 15-membered cycle can also be stretched more easily than the 18-membered one [10,19]. However, contrary to the behavior of all-oxygen analogs **3** and **4**, the compounds **6** and **7** show no contraction effect. The relative population of conformers for **7** (Table **1**) is practically the same as for *trans*-1-methylthio-2-methoxycyclohexane (n_A = 33%, $\Delta G_{\mathbf{B-A}}$ = -1.8 kJ/mol in CCl_4 [39]). For **6** the diaxial form **A** is even more populated [10,19]. Thus, sulfur-containing macrocycles appear to be more flexible (stretchable) than their oxygen analogs. This feature can be overcome by additional structural fragments, e.g. endocyclic ester groups. For example, the conformation **B** dominates very strongly for thiacrowns based on the *trans*-1,2-bis(acyloxy)cyclohexane moiety [15,16,19].

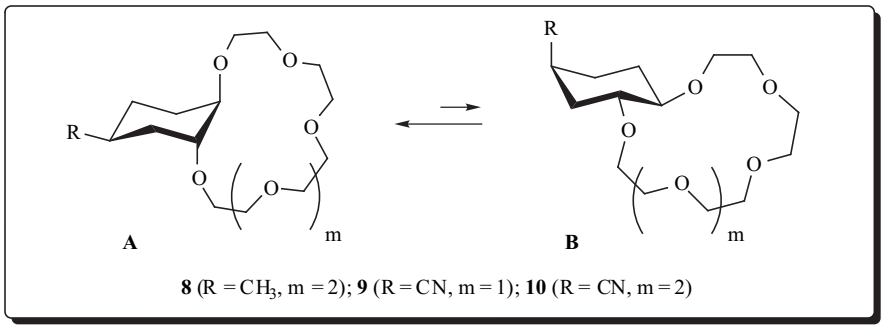
CONFORMATIONAL COUNTERBALANCES, LEVERS AND LOCKS

The well known preference for equatorial position of substituents at the cyclohexane ring [40-42] can be used to control the equilibrium of the type **1A** $\rightleftarrows$ **1B** [6-9,11,14,15,19-25,28-30]. Thus, a significant shift to the conformer **A** was observed for cyclohexano crown compounds **8-10** with methyl or cyano 'counterbalances', or 'levers' properly attached to the six-membered cycle (Table **1**) [6,7,9,11]. An axial methyl group relatively destabilizes the conformer **B** by at least 8 kJ/mol [6], which is larger than the conformational energy of methylcyclohexane, 7.3 kJ/mol [41,42]. A cyano group shifts the equilibrium for **9** and **10** with a power of 9 kJ/mol [9], which is much stronger than its conformational energy, 1 kJ/mol [40,41]. This non-additivity may be caused by intramolecular electrostatic interactions and six-membered cycle distortions. Similar observations were made for various *trans*-1,2-$(RO)_2$-*cis*-4-R'-cyclohexanes [14,15,23-25,43-45], including cyclohexanopodands [14,23-25].

The contraction effect in more rigid structures **11-13** is so strong that the conformer **A** with a stretched macrocycle becomes a predominant one only for 18-membered dithiacrown **13** with a bulky *tert*-butyl counterbalance (Table **1**) [15,19]. In contrast with the simpler analogs described above, the larger macrocycle in **13** is more flexible than the smaller one in **11** [15,19].

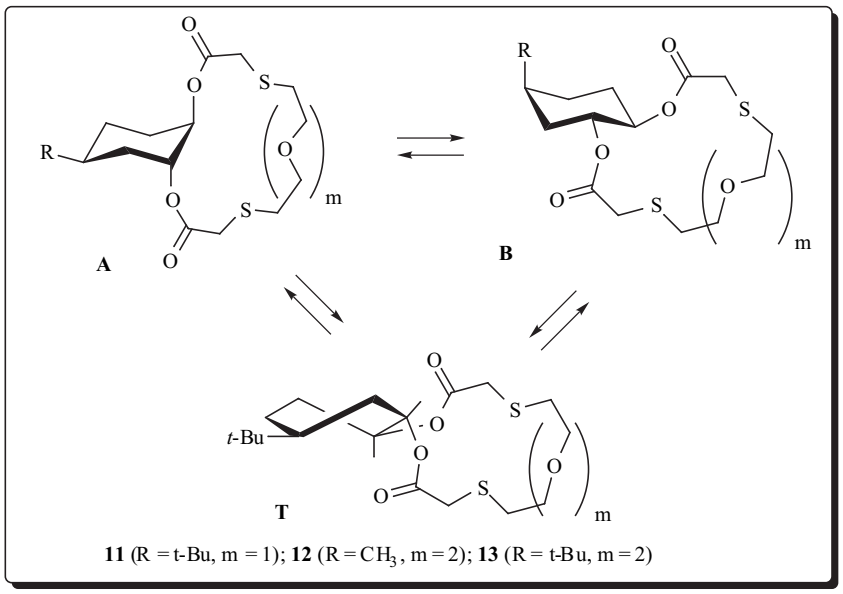
In the case of *tert*-butyl derivatives, the conformers with a twist-form of the six-membered cycle may provide a reasonable alternative to conformer **B** with comparable conformational strain [11,15,25]. Thus, a flexibility of cyclohexane ring sets a natural limit to the effective power of conformational tools (levers, locks, counterbalances) in such systems. If the power applied to both ends of the system exceeds the energy difference between the chair and twist-forms of cyclohexane (23-26 kJ/mol [41]), e.g. when R = *tert*-butyl, or a larger group, then the ring may be screwed.

Similarly, the counterbalances R force the cyclohexano podands **14-17** to adopt predominantly the conformation **A**



[22,23,25]. An interesting change of conformational preference was described for the podands **16** and **17** [23,25]. The conformer **16A** completely dominates in equilibrium due to the bulky ethylene acetal group R, but the conformer **17B** becomes a reasonable alternative when R is hydrolyzed into a smaller acetyl group.

[1] For the X-ray crystal structure of a cyclohexano-18-crown-6 derivative in a stretched conformation **A** see Refs. 29,30. For the structure of a cyclohexano crown ether in conformation **B** see Ref.12.

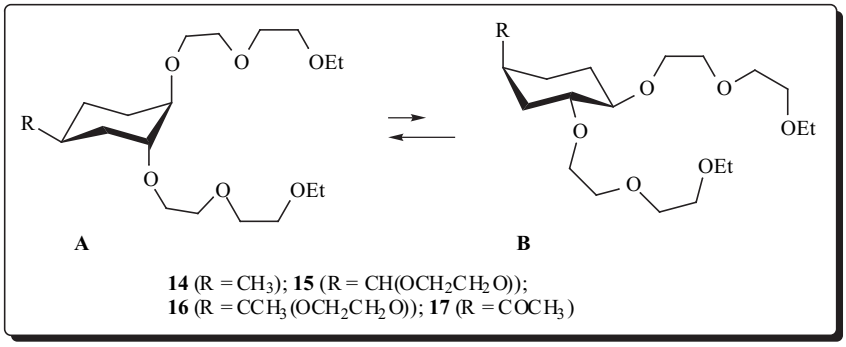


11 (R = t-Bu, m = 1); **12** (R = CH_3, m = 2); **13** (R = t-Bu, m = 2)

More than one substituent may be used to shift the equilibrium. For instance, two axial ethoxycarbonyl groups destabilize the conformer **19B** by 7-10 kJ/mol compared to **18B** (Table **1**) [14,19]. A very small contraction effect of the macrocycle (0.5-1 kJ/mol) was observed for these structures, which can be convenient intermediate models on the way to allosteric systems described further.

COMPLEXATION-INDUCED CONFORMATIONAL SWITCHES

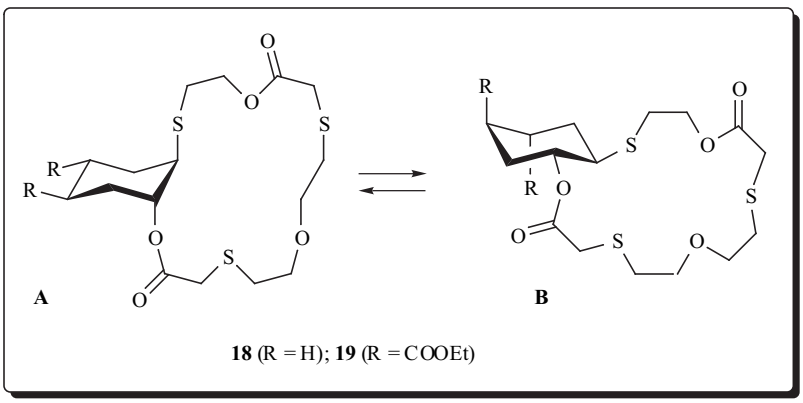
The *trans*-diaxial orientation of the C-O (or C-S) bonds in **A** conformers of the crown ethers and podands described above makes complex formation with metal ions impossible. For instance, the 'conformationally switched-off' ionophore **21** exhibited negligible transport of potassium picrate through a methylene chloride membrane after 30 days [25], and no complex formation was detected by NMR for podand **16** [23,25]. By contrast, the diequatorial direction of these bonds in **B** conformers corresponds to an *endo*-dentate orientation of heteroatoms, which is necessary for cation complexation [46,47]. Thus, the conformational flip **A** → **B** is required for the effective



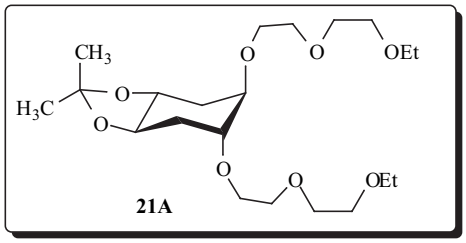
14 (R = CH_3); **15** (R = $CH(OCH_2CH_2O)$);
16 (R = $CCH_3(OCH_2CH_2O)$); **17** (R = $COCH_3$)

The predominance of conformer **A** was also observed for the structurally analogous bis(ethoxycarbonyl)cyclohexano-18-crown-6 (**20**) [28].

An ultimate bias of the equilibrium was achieved in structure **21** with a five-membered acetal conformational lock, which can be 'unlocked' by acidic hydrolysis [25].



18 (R = H); **19** (R = COOEt)



21A

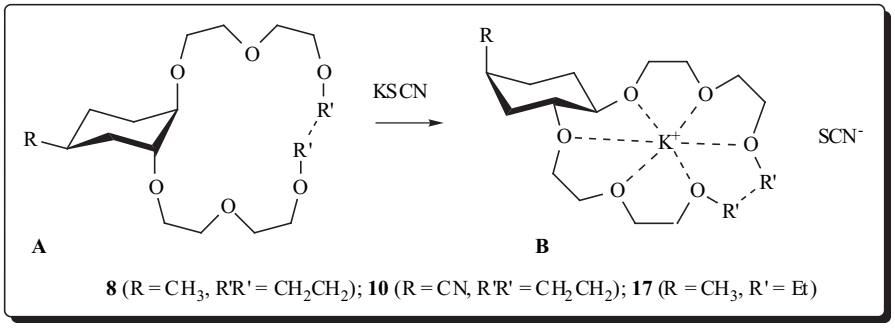
binding of cations by *trans*-cyclohexano crown compounds and podands, if they predominantly exist in the **A** conformation. This additional effort must affect the complexation/ionophore ability. Indeed, the dependence of membrane activity on the size of the alkyl group, in addition to the dependence on the size of macrocycle, was observed for a series of *cis*-4-alkyl-*trans*-cyclohexanocrown ethers studied as sensor materials in PVC-matrix membranes of ion-selective electrodes [11].

A large enough binding energy may overcome the conformational energy of group(s) R, and the conformational switch **A** → **B** should occur in the course of complexation. Thus, the binding site of these molecules (a macrocycle or a podand) is a potent conformational trigger. Such a switch into conformer **B** with an unfavorable axial position of group R was studied by ^{1}H and ^{13}C NMR for the interaction of compounds **8** [6], **10** [8], and **17** [23,25] with sodium and potassium salts, and of compound **22** with $Ca(SCN)_2$ [24]. Structurally similar ligands were used for the chelation of radioactive ^{153}Sm, but their conformations have not been studied [48].

In the ^{1}H NMR spectrum of the complex **10**·KSCN in $(CD_3)_2CO$ we were able to observe all individual signals of the cyclohexane protons, and unambiguously proved, by the values of their vicinal spin-spin coupling, the chair form of the six-membered cycle, the equatorial orientation of the attached oxygen atoms, and the axial position of the cyano group [8]. The chair form of cyclohexane moiety with the expected orientation of all substituents was also found by X-ray analysis for the complex **20**·$Hg(SCN)_2$ [28].

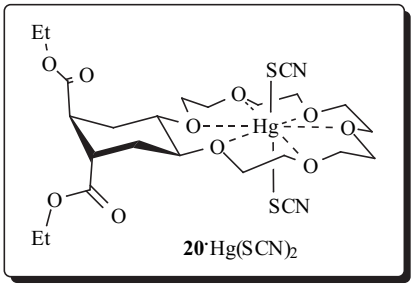
Even without the counterbalancing group(s) R, some cyclohexanocrown thioethers adopt predominantly the diaxial conformation mostly due to *gauche*-repulsion of sulfur atoms [49,50]. However, they have to switch to diequatorial conformation **B** in complexes, as was shown for *trans*-cyclohexanotetrathio-14-crown-4 [49].

Since the axial group(s) R destabilize the complexing conformer **B** compared to unsubstituted analogs, one could expect a stronger binding with cations for the latter. The data available for the complexation of *trans*-cyclohexano-18-crown-6 (**4**) and its bis(ethoxycarbonyl) derivative **20** with sodium and potassium picrates [28] do not seem to support this hypothesis. The ligand **20** demonstrates a stronger binding, which has not received an explanation [28]. Probably, this is an effect of the additional attraction between polar ester groups and a cation, similar to the interactions in pendant crown complexes. Obviously, the alkyl groups R would provide better models for the future studies.

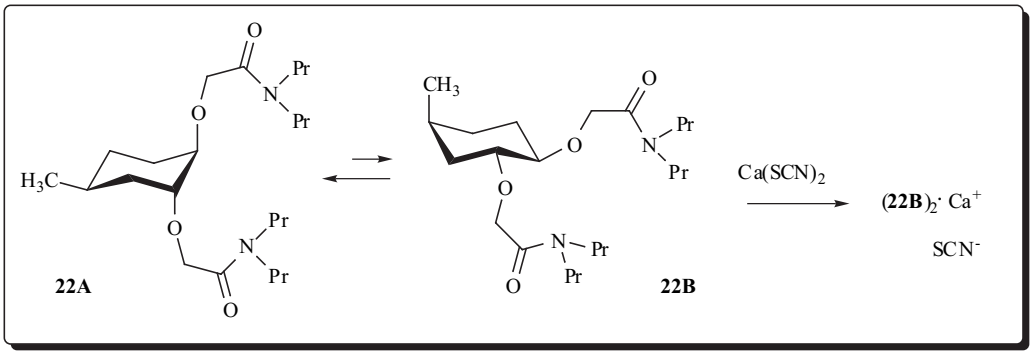


A **B**

8 (R = CH_3, R'R' = CH_2CH_2); **10** (R = CN, R'R' = CH_2CH_2); **17** (R = CH_3, R' = Et)



20·$Hg(SCN)_2$

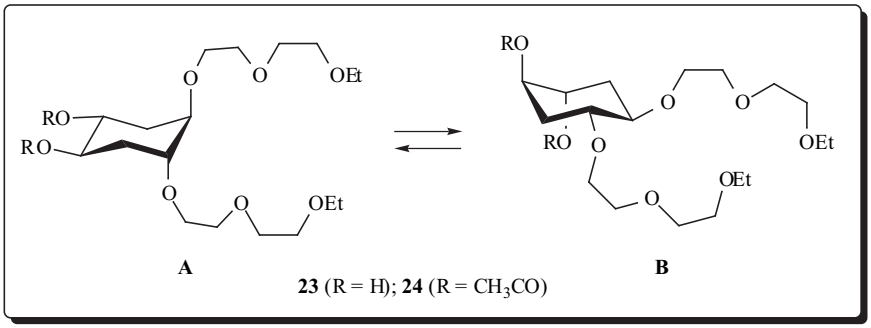


22A **22B**

HYDROGEN BOND LOCKS AND pH-INDUCED CONFORMATIONAL SWITCHES

A change by external influence of non-bonded interactions between groups W and Z in structures **1**, or between groups R in structures similar to **19**, should change the relative stability of conformers. By affecting these interactions one can control the position of conformational equilibrium of the type **1A** $\rightleftarrows$ **1B**, thus controlling the complexing ability of the macrocycle or podand.

trans-1,2-Cyclohexanediol and *trans*-2-aminocyclohexanols are well known to strongly prefer the diequatorial conformation, in part due to intramolecular hydrogen bonding between vicinal substituents [18,38,51-53]. These structural moieties can be used as conformational counterbalances or locks. Such a bias to the conformation **23A** resulted in a negligible transport of potassium picrate through the methylene chloride membrane by the dihydroxypodand **23**, comparable to the case of conformationally



locked structure **21**. A much faster transport was performed by the more balanced podand **24**, which did not have a hydrogen bonding between the groups OR (k_{24}/k_{23} = 180) [25].

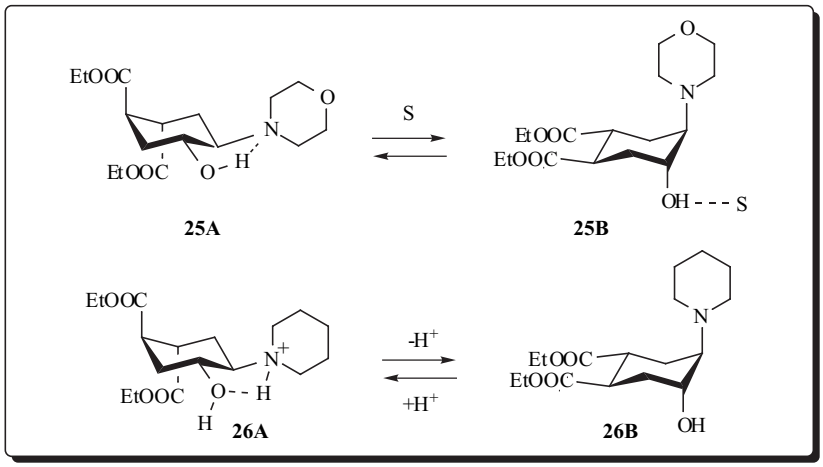
We found [18] that the *trans*-2-morpholinocyclohexanol derivative **25** adopted predominantly conformation **25A** in $CDCl_3$, but conformation **25B** in methanol or DMSO.

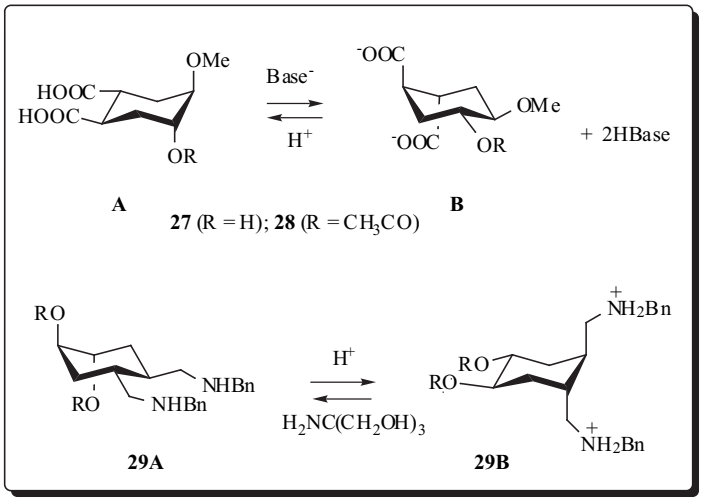
This dramatic change, which exceeded 10 kJ/mol in terms of the relative conformational stability, was attributed to destruction of the stabilizing intramolecular OH···N hydrogen bond in **25A** by the hydrogen bond acceptor solvents [18]. Similar results were obtained earlier for *trans*-2- *o*-tolyl- *cis* -4- hydroxy (amino) -*trans*-5-amino (hydroxy) cyclohexanols [51] and some other *trans*-2-aminocyclohexanols [52]. Thus, the *trans*-2-aminocyclohexanol moiety provides a promising type of a rapid conformational lock/ trigger.

Another way to control such a conformational equilibrium is an addition of acid to protonate the amino group, and to generate a possibly stronger intramolecular hydrogen bond of O···H-N^+ type, e.g. in **26A** [20,21] (see also [51]). The hydrogen bonds of both types are known to be strong enough to convert a chair ring into a twist conformation in *trans*-aminohydroxy steroids [54,55] and other conformationally locked structures [53].

Two carboxylic groups (**1**, W = Z = COOH) provide yet another promising model for such a 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 (^{1}H NMR) for compounds **27** and **28** as ≥ 10 kJ/mol [17].

In contrast with the switches described above, the protonation of two neighbouring amino groups causes an electrostatic repulsion, which moves them away into opposite axial positions, e.g. in **29B** [30]. The presence of bases able to form hydrogen bonds, such as $H_2NC(CH_2OH)_3$, stabilizes the alternative conformation **29A** with the aminomethyl groups in *trans*-diequatorial positions [30].





The conformational triggers considered in this section can be used for pH-induced conformational switching capable of changing the preferred conformation of various complexing agents thereby modifying their complexing ability.

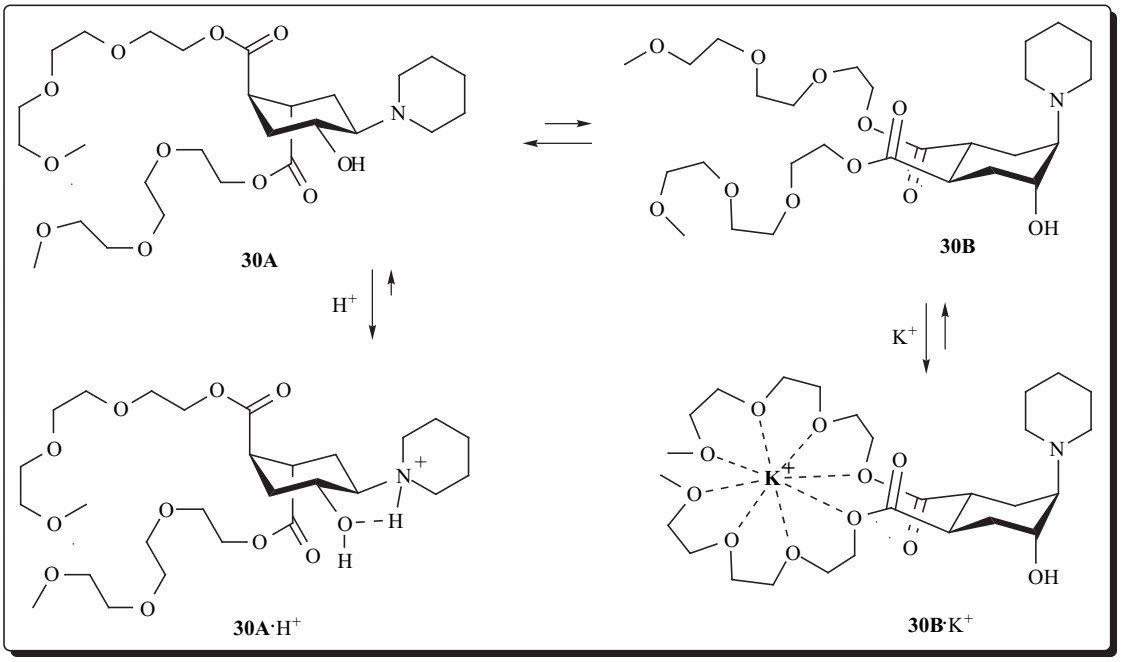
ALLOSTERIC CYCLOHEXANE-BASED SYSTEMS

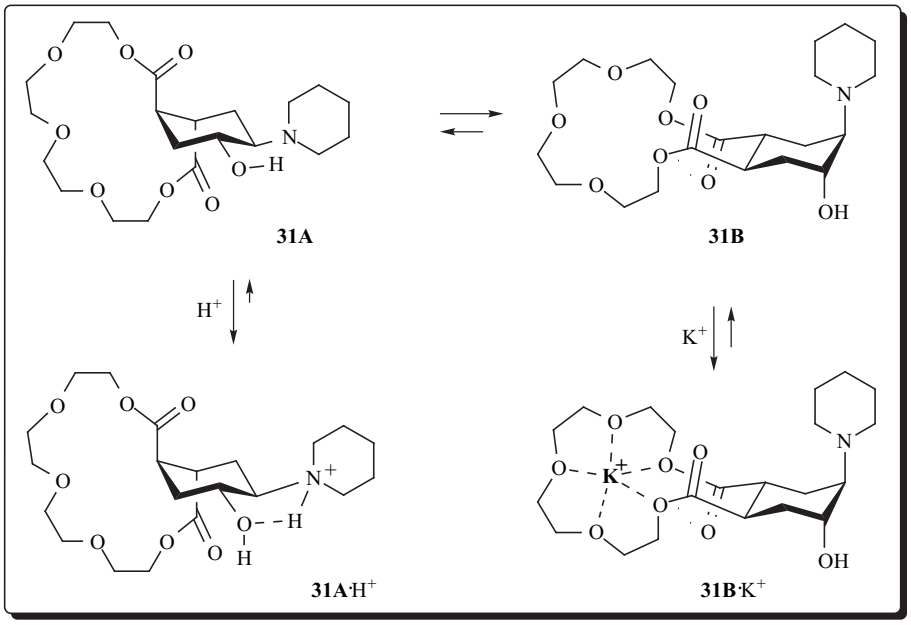
The most thoroughly studied small allosteric ligands are the structures based on biphenyl or bipyridyl molecules [56,57]. The conformational change is the rotation around a single bond, and these structures exhibit *positive* cooperativity. A very special mechanics of the cyclohexane ring allows the development of new heterotropic allosteric systems of the type **1A** $\rightleftarrows$ **1B** with high *negative* cooperativity.

We studied the conformations of such an allosteric system with *trans*-2-aminocyclohexanol moiety as a pH-trigger [20,21]. The measurement of averaged coupling constants in ^{1}H NMR has shown that the conformation **30A** is somewhat preferred for the podand **30** (Table **1**). By contrast, the crown ether **31** prefers the conformation **31B** with both ester groups equatorial. This is apparently yet another manifestation of the contraction effect of the macrocycle (see above).

As expected, both structures demonstrate a dramatic switch to **A** conformation with excess acid [20,21]. The power of this conformational trigger has been estimated from the measurements for compound **31** as ≥10.5 kJ/mol.

Possessing two different binding sites, these compounds are interesting models for a negative allosteric effect. The macrocycle in **31** and polyether chains in **30** should be able to form complexes with metal ions. Only conformations **30B** and **31B** provide the necessary geometrical arrangement for such complexation. Indeed, the conformational equilibria were shifted to these conformations when methanolic solutions of **30** or **31** were saturated with KI [20,21]. This effect was not strong – approximately 1.5-2 kJ/mol. Addition of excess acetic acid to these solutions completely switched the equilibrium back to alternative conformations



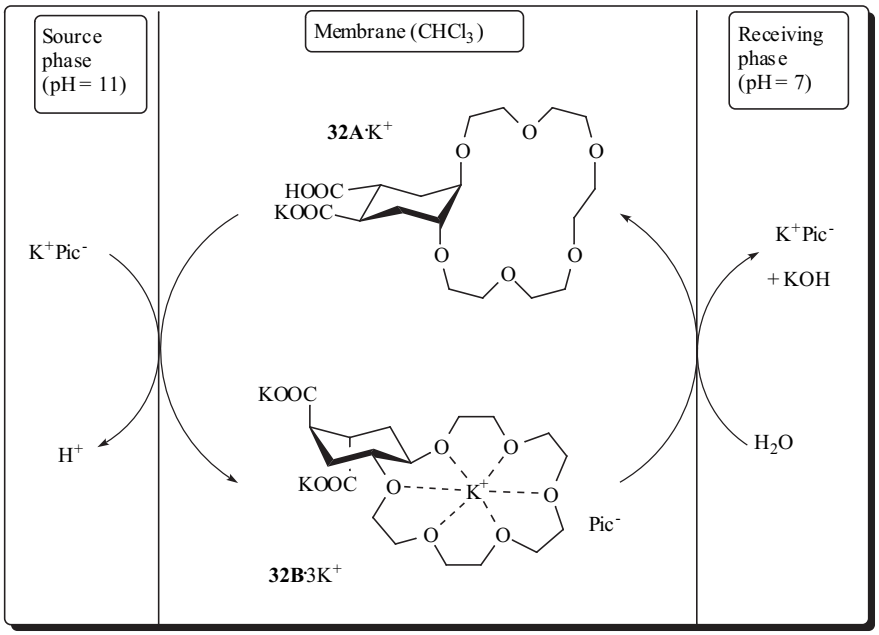


30A and **31A**. The conformational equilibrium for the related non-complexing compound **26** was reasonably indifferent to the addition of potassium salt [20,21].

The *trans*-1,2-cyclohexanedicarboxylic acid moiety, proposed by us as a conformational pH-trigger (see above) [17], has been employed by other researchers to modify the complexing ability of *trans*-cyclohexano-18-crown-6 [29,30]. Compound **32**, whose conformational state depended strongly on pH [29], was studied as a cation carrier in the liquid membrane transport [30]. The efficiency of transport increased along with the increase of the source phase pH, apparently due to the conformational switch into the complexing form **32B** caused by deprotonation.

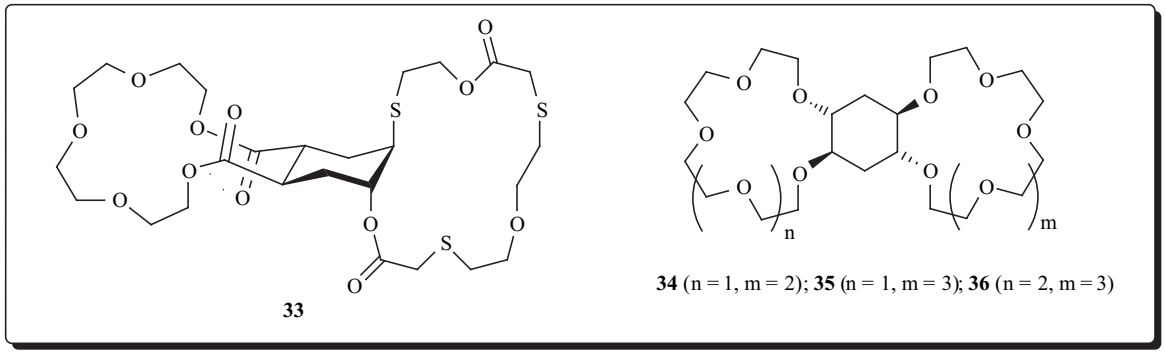
Similar experiments with diamino crown ether **29** (R,R = $-CH_2(CH_2OCH_2)_4CH_2-$) produced rather inconsistent results, although the sensitivity of membrane transport to the pH of the aqueous phases was evident [30]. Regrettably, when the authors varied pH of the aqueous phases, they did not try an acidic source phase that could switch **29** into complexing form **29B**.

The concept of a heterotropic cyclohexano-*bis*-crown compound with a negative allosterism (e.g. **33**) was first proposed by us in 1990-91.[2]



Using the synthetic procedures developed for trans-cyclohexano crown ethers [5,7,10,11], Costero *et al.* [26,27] prepared and studied different, all-oxygen bis-crown ethers **34-36**.

[2] Samoshin, V. V.; Zelenkina, O. A.; Zapolskii, M. E.; Vereshchagina, Ya, A.; Zefirov, N. S. The conformationally controlled crown ethers. In *Abstr. of 15th Internat. Symp. on Macrocyclic. Chem*., Odessa, USSR, 1990, p.182; Samoshin, V. V.; Zefirov, N. S. The conformationally controlled crown ethers. In *Abstr. of 16th Internat. Symp. on Macrocyclic Chem*., Sheffield, UK, 1991, p.ST30.



33

34 (n = 1, m = 2); **35** (n = 1, m = 3); **36** (n = 2, m = 3)

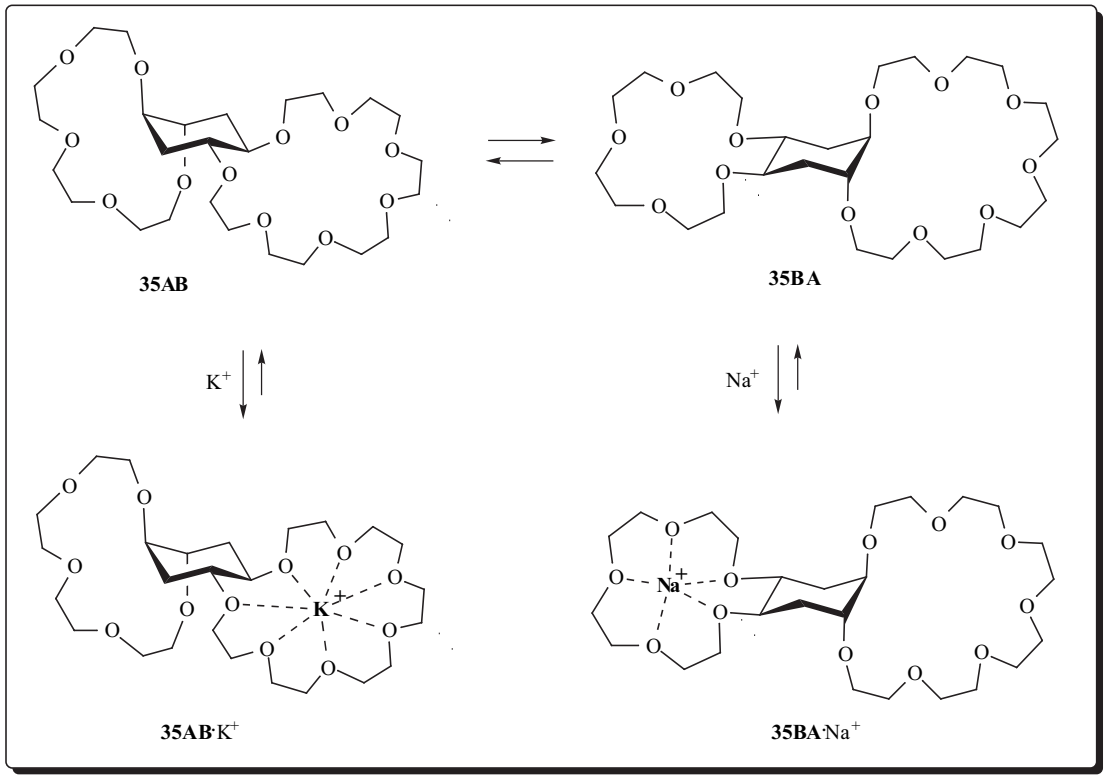
The association constants and the relative rates of membrane transport revealed a negative allosteric cooperativity in these systems [26,27]. Thus, the association constants with Na^+ and K^+ are significantly lower for **35** and **36** compared to equivalent mixtures of the corresponding mono-crown ethers (e.g. **3** *and* **4**). This may be a result of the conformational equilibrium **AB** $\rightleftharpoons$ **BA**, where each macrocycle spends some time in a non-complexing conformation.

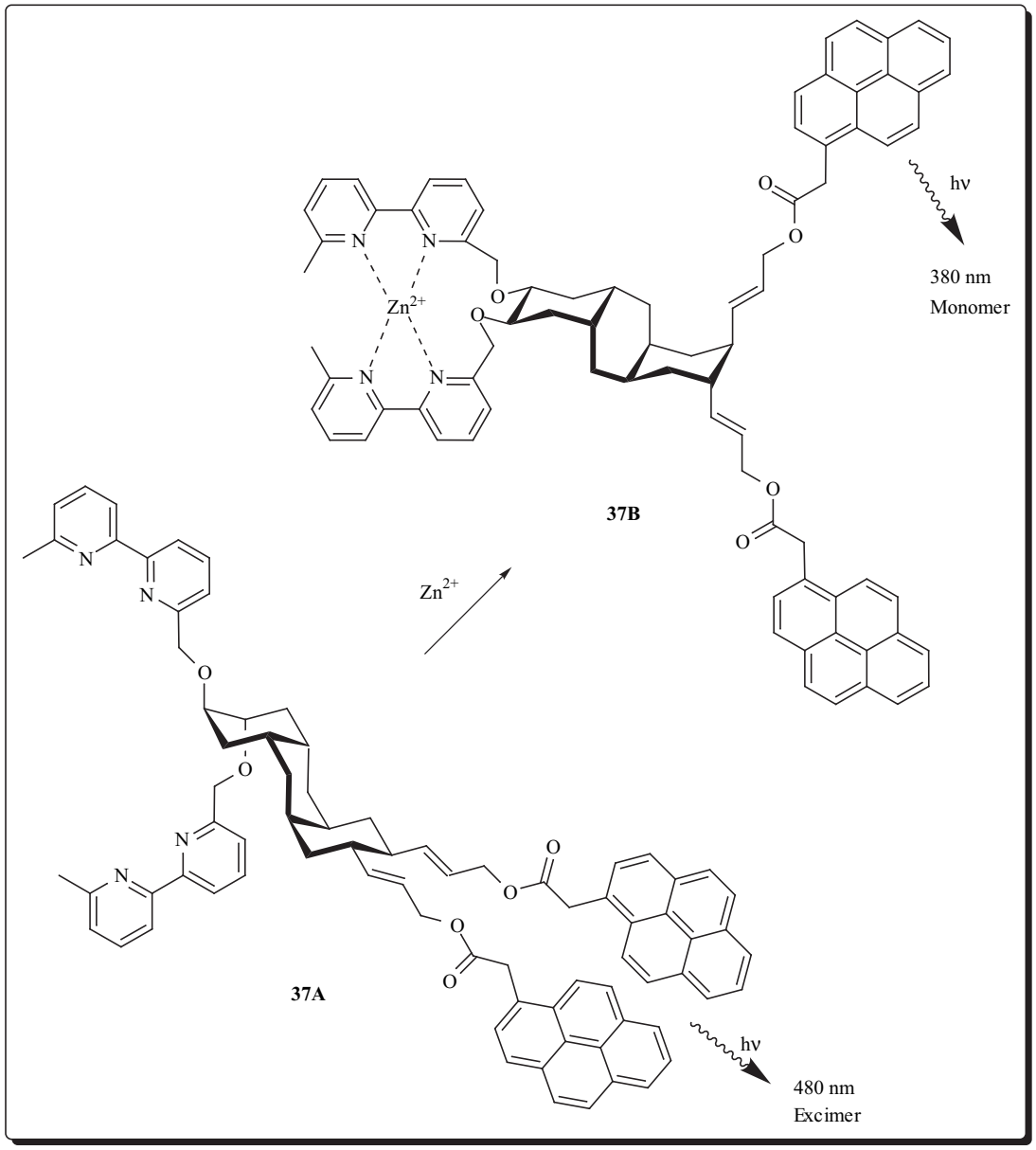
Moreover, the bis-crown ether **35** is able to simultaneously transport through a chloroform membrane twice as much of Na^+ and K^+ (in opposite directions) as the two corresponding mono-crown ethers added together [26,27]. Apparently, when the complex **35AB**·K^+ arrives at the interface with the NaCl solution, complexation with Na^+ occures that forces the carrier to switch conformation to **35BA**·Na^+, thus releasing K^+, and *vice versa* [26,27]. This allosteric mechanism increases membrane transport in both directions and provides a simple model for the Na^+-K^+ pump.

DECALIN- AND PERHYDROANTHRACENE-BASED CONFORMATIONAL TRANSMITTORS

A conformational impulse can be transmitted over a larger distance if the cyclohexane transmitting unit is extended by additional units as in *cis*-decalin or *cis-anti-cis*-perhydroanthracene [31-36]. Similar to cyclohexane, these structures have two low energy chair conformations that can switch when the attached binding groups interact with a guest.

Thus, the NMR analysis of compound **37** revealed [32,34,36] that the conformer **37A** was the only detectable species. The fluorescence spectrum of **37A** displayed the expected strong excimer band at 480 nm and the weak monomer band at 380 nm. In a complex with $Zn(OTf)_2$, the conformational switching to form **37B** occurred, resulting in decrease of the excimer band intensity compared to that of the monomer band. Reversibility of the switch was achieved by addition of competitive chelating agents (e.g. EDTA), resulting in the relative increase of the pyrene excimer emission [32,34,36].





By analogy with the principle of 'vinylogy', such a transmission of a (conformational) effect through additional repeating structural units could probably be named a principle of 'cyclohexanology'. Then, the decalin and perhydroanthracene moieties would be called 'cyclohexanologs'.

CONCLUSION

Only very preliminary studies have been done so far on cyclohexane-based conformationally controlled crowns and podands. However, the few available examples described in this review attest to the potential importance of this emerging new class of molecular switches.

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REFERENCES

[1] *Molecular switches*; Feringa, B. L., Ed.; Wiley-VCH: Weinheim, Chichester, **2001**.

[2] Schneider, H.-J.; Yatsimirsky, A. *Principles and Methods in Supramolecular Chemistry*; Wiley: Chichester, New York, **2000**.

[3] Takeuchi, M.; Ikeda, M.; Sugasaki, A.; Shinkai, S. *Acc. Chem. Res.* **2001**, *34*, 865.

[4] Samoshin, V. V.; Subbotin, O. A.; Zelenkina, O. A.; Zefirov, N. S. *Zh. Org. Khim.* **1986**, *22*, 2231 (*Russ. J. Org. Chem.* **1986**, *22*, 2004).

[5] Samoshin, V. V.; Zelenkina, O. A.; Subbotin, O. A.; Zefirov, N. S. *Zh. Org. Khim.* **1987**, *23*, 1319 (*Russ. J. Org. Chem.* **1987**, *23*, 1192).

[6] Samoshin, V. V.; Zelenkina, O. A.; Yartseva, I. V.; Zefirov, N. S. *Zh. Org. Khim.* **1987**, *23*, 2244 (*Russ. J. Org. Chem.* **1987**, *23*, 1984).

[7] Samoshin, V. V.; Zelenkina, O. A.; Subbotin, O. A.; Sergeev, N. M.; Zefirov, N. S. *Zh. Org. Khim.* **1988**, *24*, 465 (*Russ. J. Org. Chem.* **1988**, *24*, 413).

[8] Samoshin, V. V.; Yartseva, I. V.; Zelenkina, O. A.; Zefirov, N. S. *Zh. Org. Khim.* **1988**, *24*, 2455 (*Russ. J. Org. Chem.* **1988**, *24*, 2215).
[9] Samoshin, V. V.; Zelenkina, O. A.; Yartseva, I. V.; Subbotin, O. A.; Zefirov, N. S. *Zh. Org. Khim.* **1988**, *24*, 2458 (*Russ. J. Org. Chem.* **1988**, *24*, 2217).
[10] Samoshin, V. V.; Zapol'skiy, M. E.; Lutsenko, A. I.; Zelenkina, O. A.; Zefirov, N. S. *Zh. Org. Khim.* **1989**, *25*, 651 (*Russ. J. Org. Chem.* **1989**, *25*, 586).
[11] Tsingarelli, R. D.; Shpigun, L. K.; Samoshin, V. V.; Zelyonkina, O. A.; Zapolsky, M. E.; Zefirov, N. S.; Zolotov, Y. A. *Analyst* **1992**, *117*, 853.
[12] Potekhin, K. A.; Struchkov, Y. T.; Konoplyanko, N. V.; Samoshin, V. V.; Zefirov, N. S. *Dokl. Akad. Nauk USSR* **1992**, *326*, 1007 (*Proc. Acad. Sci. USSR* **1992**, *326*, 240).
[13] Samoshin, V. V.; Konoplyanko, N. V.; Lutsenko, A. I.; Zefirov, N. S. *Zh. Org. Khim.* **1992**, *28*, 867 (*Russ. J. Org. Chem.* **1992**, *28*, 668).
[14] Samoshin, V. V.; Vereshchagina, Y. A.; Konoplyanko, N. V.; Lutsenko, A. I.; Zefirov, N. S. *Zh. Org. Khim.* **1993**, *29*, 213 (*Russ. J. Org. Chem.* **1993**, *29*, 183).
[15] Samoshin, V. V.; Vereshchagina, Y. A.; Lutsenko, A. I.; Zefirov, N. S. *Zh. Org. Khim.* **1993**, *29*, 1095 (*Russ. J. Org. Chem.* **1993**, *29*, 910).
[16] Troyansky, E. I.; Ismagilov, R. F.; Samoshin, V. V.; Strelenko, Y. A.; Demchuk, D. V.; Nikishin, G. I.; Lindeman, S. V.; Khrustalev, V. N.; Struchkov, Y. T. *Tetrahedron* **1995**, *51*, 11431.
[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.
[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 (*Russ. J. Org. Chem.* **1996**, *32*, 1066).
[19] Samoshin, V. V.; Troyansky, E. I. *Phosph., Sulf., Silicon* **1997**, *120/121*, 181.
[20] Samoshin, V. V.; Chertkov, V. A.; Gremyachinskiy, D. E.; Dobretsova, E. K.; Shestakova, A. K.; Vatlina, L. P. *Tetrahedron Lett.* **2004**, *45*, 7823.
[21] Samoshin, V. V.; Gremyachinskiy, D. E.; Chertkov, V. A.; Brazdova, B.; Dobretsova, E. K.; Shestakova, A. K.; Vatlina, L. P.; Schneider, H.-J. *ARKIVOC* **2005**, accepted for publication.
[22] Raban, M.; Hortelano, E.; Quin, J.; King, N.; Koch, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1557.
[23] Raban, M.; Quin, J.; Belguise, A. *Tetrahedron Lett.* **1991**, *32*, 35.
[24] Raban, M.; Burch, D. L.; Hortelano, E. R.; Durocher, D. *J. Org. Chem.* **1994**, *59*, 1283.
[25] Raban, M.; Quin, J.; Belguise, A.; Durocher, D.; Kost, D. *Chirality* **1998**, *10*, 78.
[26] Costero, A. M.; Rodriguez, S. *Tetrahedron Lett.* **1992**, *33*, 623.
[27] Costero, A. M.; Rodriguez, S. *Tetrahedron* **1992**, *48*, 6265.
[28] Costero, A. M.; Villarroya, J. P.; Gil, S.; Aurell, M. J.; de Arellano, M. C. R. *Tetrahedron* **2002**, *58*, 6729.
[29] Costero, A. M.; Villarroya, J. P.; Gil, S.; Gavina, P.; Ramirez De Arellano, M. C. *Supramol. Chem.* **2003**, *15*, 403.
[30] Costero, A. M.; Villarroya, J. P.; Gil, S.; Martinez-Manez, R.; Gavina, P. *C. R. Chimie* **2004**, *7*, 15.
[31] Berninger, J.; Krauss, R.; Weining, H.-G.; Koert, U.; Ziemer, B.; Harms, K. *Eur. J. Org. Chem.* **1999**, 875.
[32] Krauss, R.; Weining, H.-G.; Seydack, M.; Bendig, J.; Koert, U. *Angew. Chem., Int. Ed.* **2000**, *39*, 1835.
[33] Koert, U.; Krauss, R.; Weining, H.-G.; Heumann, C.; Ziemer, B.; Mügge, C.; Seydack, M.; Bendig, J. *Eur. J. Org. Chem.* **2001**, 575.
[34] Weining, H.-G.; Krauss, R.; Seydack, M.; Bendig, J.; Koert, U. *Chem. Eur. J.* **2001**, *7*, 2075.
[35] Karle, M.; Bockelmann, D.; Schumann, D.; Griesinger, C.; Koert, U. *Angew. Chem., Int. Ed.* **2003**, *42*, 4546.
[36] Krauss, R.; Koert, U. *Synlett* **2003**, 598.
[37] Samoshin, V. V.; Troyansky, E. I.; Demchuk, D. V.; Ismagilov, R. F.; Chertkov, V. A.; Lindeman, S. V.; Khrustalev, V. N.; Struchkov, Y. T. *J. Phys. Org. Chem.* **1998**, *11*, 241.
[38] Zefirov, N. S.; Samoshin, V. V.; Subbotin, O. A.; Baranenkov, V. I.; Wolfe, S. *Tetrahedron* **1978**, *34*, 2953.
[39] Zefirov, N. S.; Gurvich, L. G.; Shashkov, A. S.; Krimer, M. Z.; Vorob'eva, E. A. *Tetrahedron* **1976**, *32*, 1211.
[40] Jensen, F. R.; Bushweller, C. H. *Adv. Alicycl. Chem.* **1971**, *3*, 139.
[41] Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of organic compounds*; Wiley: New York, **1994**.
[42] Booth, H.; Everett, J. R. *J. Chem. Soc., Chem. Commun.* **1976**, 278.
[43] Zefirov, N. S.; Zelenkina, O. A.; Subbotin, O. A.; Samoshin, V. V. *Zh. Org. Khim.* **1987**, *23*, 1122 (*Russ. J. Org. Chem.* **1987**, *23*, 1013).
[44] Zefirov, N. S.; Samoshin, V. V.; Subbotin, O. A.; Zemlyanova, T. G.; Akhmetova, G. M. *Zh. Org. Khim.* **1987**, *23*, 1320 (*Russ. J. Org. Chem.* **1987**, *23*, 1193).
[45] Kost, D.; Peor, N.; Sod-Moriah, G.; Sharabi, Y.; Durocher, D. T.; Raban, M. *J. Org. Chem.* **2002**, *67*, 6938.
[46] Cooper, S. R. *Acc. Chem. Res.* **1988**, *21*, 141.
[47] Blake, A. J.; Schroeder, M. *Adv. Inorg. Chem.* **1990**, *35*, 1.
[48] Loussouarn, A.; Duflos, M.; Benoist, E.; Chatal, J.-F.; Le Baut, G.; Gestin, J.-F. *J. Chem. Soc., Perkin Trans. 1* **1998**, 237.
[49] Desper, J. M.; Vyvyan, J. R.; Mayer, M. J.; Ochrymowycz, L. A.; Gellman, S. H. *Inorg. Chem.* **1993**, *32*, 381.
[50] Arkhipov, A. Y.; Chertkov, V. A.; Samoshin, V. V.; Anisimov, A. V. *Khim. Geterotsikl. Soed.* (*Chem. Heterocycl. Comp.*) **1996**, 564.
[51] Whelton, B. D.; Lowry, B. R.; Carr, J. B.; Huitric, A. C. *J. Pharm. Sci.* **1973**, *62*, 728.
[52] Tichy, M. *Coll. Czech. Chem. Commun.* **1973**, *38*, 3631.
[53] Longevialle, P.; Girard, J.-P.; Rossi, J.-C.; Tichy, M. *Org. Mass Spec.* **1980**, *15*, 268.
[54] Schneider, H.-J.; Buchheit, U.; Gschwendtner, W.; Lonsdorfer, M. In *Molecular Structure and Biological Activity*; Griffin, J. F., Duax, W. L., Eds.; Elsevier: New York, **1982**; pp. 165.
[55] Kooijman, H.; Kelder, J.; Kanters, J. A.; Duisenberg, A. J. M.; Kroon, J. *J.Chem.Soc., Perkin Trans. 2* **1996**, 2133.
[56] Costero, A. M. In *Recent Research Developments in Organic Chemistry* **2000**; Vol. *4*, pp. 133.
[57] Gavina, F.; Luis, S. V.; Costero, A. M.; Burguete, M. I.; Rebek, J. Jr. *J. Am. Chem. Soc.* **1988**, *110*, 7140

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