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trans-2-(Azaarylsulfanyl)cyclohexanol derivatives as potential pH-triggered conformational switches

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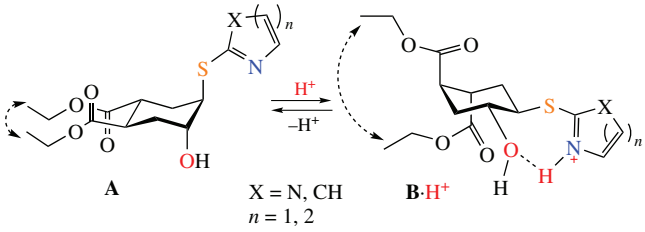
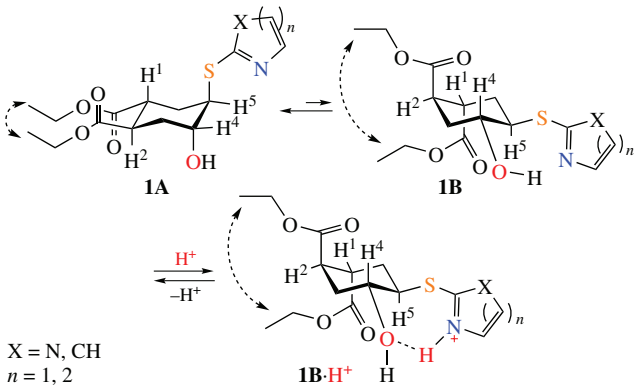
A series of *trans*-2-(azaarylsulfanyl)cyclohexanol derivatives, structurally similar to previously studied *trans*-2-amino-cyclohexanols, were synthesized through epoxide ring opening under basic conditions with sodium tetraborate as a catalyst. ^{1}H NMR spectroscopy was used to elucidate the conformational equilibrium in various solvents and its acid-induced change due to stabilization of the conformer with the azaarylsulfanyl and hydroxy groups in equatorial position by an intramolecular hydrogen bond and electrostatic interactions.



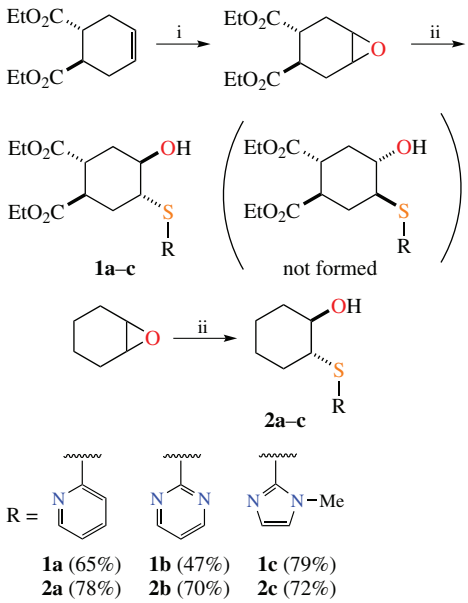
Conformational switches are molecules that can toggle between conformations reversibly when triggered by external stimuli: metal cation complexation, electric field, light at specific wavelength, pH changes, *etc*. These are useful in designing controllable compounds with a variety of functions which may include drug release, information storage and information transmission.[1–6] The cyclohexane-based molecular systems provide an efficient prototype for such devices, specifically the *trans*-2-aminocyclohexanol moiety that was successfully used in pH-triggered conformational switches.[5–7] Addition of acid to these compounds results in protonation of the amino group and formation of a strong hydrogen bond of O···H–N$^+$ type, which stabilizes the previously unstable conformer, concurrently transferring other groups on the cycle from equatorial to axial positions and resulting in a change of conformation-dependent properties. This switch was used to affect change in the interaction of molecules in the lipid bilayer of liposomes upon decrease of pH leading to perturbation of the layers and release of the drug cargo.[5,6] Alterations of the substituents on the amine nitrogen of *trans*-2-aminocyclohexanols affected the basicity of the amino group, resulting in a variety of pH-ranges within which the conformational switching occurred.[5–7]



Scheme 1

To expand the existing assortment of potential pH-triggers, we synthesized and tested a series of *trans*-2-(azaarylsulfanyl)-cyclohexanols **1** as possible conformational switches (Scheme 1). The advantage of these models could be an additional shift of conformational equilibrium towards form **A** due to a substantial repulsion of the equatorial RS and OH groups in form **B**, as was previously observed for similar structures (with not N-hetero-cyclic substituents R).[8,9] The stronger initial predominance of **A** would provide an opportunity for a wider swing towards **B** upon protonation.

The model compounds **1a–c** containing two ethoxycarbonyl groups, the azaarylsulfanyl and hydroxyl substituents, and **2a–c** containing only the azaarylsulfanyl and hydroxyl substituents



Scheme 2 *Reagents and conditions:* i, *m*CPBA, CH_2Cl_2, 0 °C, 13 h; ii, RSH, $Na_2B_4O_7 \cdot 10H_2O$, THF·H_2O, room temperature, 48–72 h.

Table 1 ^{1}H NMR data and conformational parameters for compounds **2a–c**.[a]

Compound	Solvent	H^1(O)		H^2(S)		$n_B(n^+_{BD})$ (%)	ΔG_{B-A}/kJ mol^{-1}
		δ	W/Hz	δ	W/Hz		
2a	$CDCl_3$	3.52	24.8[b]	3.42	26.7[b]	~100	⩽–10
2a	$(CD_3)_2SO$	3.44	~21.7[c]	3.66	22.3	75	–2.7
2a	CD_3OD	3.51	~22.5[d]	3.54	~23.0[d]	80	–3.4
2a	$CD_3OD + CF_3CO_2D$[e]	3.62	24.7	3.56	26.1	97	–8.4
2b	$CDCl_3$	3.58	[f]	3.63	26.0	96	–7.5
2b	$(CD_3)_2SO$	3.45	~22.2[c]	3.66	22.8	79	–3.2
2b	CD_3OD	3.57	22.9	3.77	24.2	85	–4.3
2b	$CD_3OD + CF_3CO_2D$[e]	3.58	23.3	3.79	24.6	88	–4.8
2c	$CDCl_3$	3.53	24.7	2.99	26.3	97	–8.4
2c	$(CD_3)_2SO$	3.30	~23.0[c]	3.00	23.9	85	–4.2
2c	CD_3OD	3.39	23.7	2.93	24.7	89	–5.2
2c	$CD_3OD + CF_3CO_2D$[e]	3.47	24.4	3.24	26.4	97	–8.4

[a] 600 MHz; 0.02–0.03 M solutions; 294 K. [b] Used as W_B. [c] J_{HCOH} was subtracted. [d] Poorly resolved signal. [e] CF_3CO_2D was added in large molar excess (×10–15) to a CD_3OD solution. [f] Overlapped with other signals.

were synthesized by cleavage of the corresponding epoxides under basic conditions with sodium tetraborate as a catalyst (Scheme 2). Similar to previous studies,[6,7] the diastereomers **1** with the required configuration were the only isolable products. The conformational behavior of the obtained cyclohexanols **1** and **2** was evaluated under various conditions by ^{1}H NMR spectroscopy (Tables 1, 2).

The fast equilibrium [**A**] ⇄ [**B**] ⇄ [**B**·H$^+$] (see Scheme 1) was examined by ^{1}H NMR spectroscopy (600 MHz). The vicinal coupling constants $^3J_{HH}$ between several protons attached to the cyclohexane moiety are strongly conformation-dependent, which allows one to assign a predominant conformation and evaluate the position of conformational equilibrium, namely, large vicinal couplings, 9–12 Hz, are observed between the *trans*-diaxial protons, and small values, 2–5 Hz, are measured for the axial-equatorial and equatorial-equatorial vicinal couplings.[10] The observation of a single set of well-resolved multiplets with the averaged NMR parameters attests to high rates of both conformational and acid–base equilibria on the NMR time scale. The conformer populations (n_A, n_B) in dilute solutions were estimated as described previously[6,7] using Eliel's equation[11] applied to the averaged signal width $W = \Sigma J_{HH}$ (a sum of spin–spin couplings) of the protons germinal to the substituents (see Scheme 1): $W_{observed} = W_A n_A + W_B n_B$. These signals were usually well resolved and had chemical shifts in a region apart from the signals of other protons. The parameter W was measured as a distance between terminal peaks of a multiplet. The evaluated share of conformer **B** (n_B) thus includes both the non-protonated form **B** and the protonated form **B**·H$^+$ (see Scheme 1; Tables 1, 2). The limiting parameters W_A and W_B for individual conformers (Figure 1) were obtained from the measurements for compounds **1a**,**b** and **2a** (see Tables 1, 2) and from the reported data for the related cyclohexane derivatives with completely biased conformational equilibrium.[6,7] Parameter W_B value was assumed to equal 24.8 Hz for H(O) geminal to OH (see Table 1), 26.7 Hz for H(S) geminal to RS (see Table 1), and 10 Hz for H(CO_2Et) geminal to ester groups (see Table 2). Parameter W_A value was set 9.1 Hz for H(O), 11 Hz for H(S) (see Table 2), and 27.7 Hz for H(CO_2Et). Analogous data for other protons were used when possible to confirm the conformational assignment.

Table 2 ^{1}H NMR data and conformational parameters for compounds **1a–c**.[a]

Compound	Solvent	H^4(O)		H^5(S)		H^1		H^2		$n_B(n^+_{BD})$ (%)	ΔG_{B-A}/kJ mol^{-1}
		δ	W/Hz	δ	W/Hz	δ	W/Hz	δ	W/Hz		
1a	$CDCl_3$	3.81	[b]	3.81	[b]	3.13	16.2	3.25	16.5	64	–1.4
1a	$(CD_3)_2SO$	3.93	(11.3)[c]	4.19	(11.2)[c]	2.73	27.7[d]	2.93	27.8[d]	~0	⩾10
1a	CD_3OD	4.03	9.9	4.19	11.1	2.89	26.8	3.07	27.0	4	7.8
1a	$CD_3OD + CF_3CO_2D$[e]	3.92	[b]	3.92	[b]	3.09	~18.2[f]	3.24	18.9	52	–0.2
1b	$CDCl_3$	4.00	[b]	4.00	[b]	3.04	20.6	3.19	20.8	40	1.0
1b	$(CD_3)_2SO$	3.97	(11.4)[c]	4.12	~11.0[f]	2.72	27.7[d]	2.94	27.7[d]	~0	⩾10
1b	CD_3OD	4.10	~9.6[b]	4.22	11.0[d]	2.86	27.2	3.08	27.3	2	9.1
1b	$CD_3OD + CF_3CO_2D$[e]	4.10	~10.3[b]	4.23	11.0[d]	2.86	27.0	3.08	27.2	4	7.9
1c	$CDCl_3$	3.85	19.2	3.40	20.4	3.10	16.7	3.23	17.0	62	–1.1
1c	$(CD_3)_2SO$	3.84	(12.1)[c]	3.58	~10[b]	2.80	27.0	2.91	27.0	4	7.5
1c	CD_3OD	3.88	10.9	3.45	11.5	2.99	25.0	3.05	25.2	11	5.1
1c	$CD_3OD + CF_3CO_2D$[e]	3.76	18.5	3.53	19.9	3.14	17.2	3.25	17.3	58	–0.8

[a] 600 MHz; 0.02–0.03 M solutions; 294 K. [b] Partially or completely overlapped with other signals. [c] Unresolved signal (a width at 1/3 of its height is shown; it includes J_{HCOH}). [d] Used as W_A. [e] CF_3CO_2D was added in large molar excess (×10–15) to CD_3OD solution. [f] Poorly resolved signal.

All the studied *trans*-(*RS*)-cyclohexanols **2a–c** prefer to exist in the diequatorial conformation **2B** in all solvents (70–100%, see Table 1). This preference is substantially smaller than could be expected from the data for similar models with R = Me, Ph that were found to be completely diequatorial regardless of solvent and temperature.[8] Interestingly, the preference for the apparently more polar form **2B** is stronger in relatively non-polar $CDCl_3$ than in polar solvents. A plausible explanation for this difference may be an intramolecular hydrogen bond OH···N in the current *N*-hetaryl derivatives, which stabilizes **2B** in $CDCl_3$, but is interrupted by interaction with CD_3OD and especially with $(CD_3)_2SO$.

The conformational equilibrium of the molecules **1** in polar solvents is strongly shifted towards conformation **1A**, where two ethoxycarbonyl counterbalances are in equatorial positions. However, the opposite conformation **1B** is almost equally populated or even slightly predominant in non-polar $CDCl_3$, apparently because of the stabilizing intramolecular hydrogen bond (see above). Previously we estimated the destabilizing effect of two axial COOEt groups in structures similar to **1B** (with R = alkyl) as 7 to 8 kJ mol^{-1} in C_6D_{12} and approximately 10 kJ mol^{-1} in $CDCl_3$ and $(CD_3)_2CO$.[9] A comparison of the ΔG_{B-A} data in Tables 1 and 2 (**1** *vs*. **2**) gives similar values: 7.3–8.6 kJ mol^{-1} in $CDCl_3$, 12–14 kJ mol^{-1} in $(CD_3)_2SO$, and 10–13 kJ mol^{-1} in CD_3OD.

To explore the possible acid-induced shift of the conformational equilibrium, the CD_3OD solutions were treated with up to a 15-fold molar excess of CF_3COOD. Despite the already substantial conformational bias, a noticeable additional shift of equilibrium towards the diequatorial **2B**·D$^+$ was observed for the pyridinyl and imidazolyl derivatives **2a** (81 → 98%) and **2c** (90 → 98%). Unexpectedly, the equilibrium of pyrimidinyl derivative **2b** remained practically insensitive (see Table 1). Similar trend was observed for the counterbalanced systems **1** (see Table 2). The initial low content of conformers **1B** increased significantly in the presence of excess acid for **1a** (5 → 52%) and for **1c** (12 → 59%), apparently because of their stabilization in the form **1B**·D$^+$ by an intramolecular hydrogen bond of the type O···D–N$^+$ and by electrostatic attraction O···N$^+$. The equilibrium of the pyrimidinyl derivative **1b** was again insensitive to acid.

Although the studied compounds were not able to perform a full range of a conformational switch till 100% of **1B**·D$^+$, the shift of equilibrium by ~50% is of the same magnitude as the one performed by the majority of structurally similar *trans*-2-aminocyclohexanols studied previously.[6,7] The obvious dependence of the sensitivity to acid on the structure of *N*-hetaryl group motivates for further studies of these promising models.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.09.005.

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