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EXPLORATION OF NEW *trans*-2-AMINOCYCLOHEXANOL DERIVATIVES AS POTENTIAL pH-TRIGGERED CONFORMATIONAL SWITCHES

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Abstract

A new series of *trans*-2-aminocyclohexanols have been synthesized and explored as conformational pH-triggers. The conformational equilibrium and its possible pH-induced change due to an intramolecular hydrogen bond and electrostatic interactions were studied by ^{1}H NMR spectroscopy. The position of equilibrium depends on substituents and on solvent. Such acid-induced transition may be used to control the geometry-dependent molecular properties. The ^{1}H NMR titration curves were used for estimation of the pKa values of protonated compounds that varied from 7.4 to 2.5 (in CD_3OD) depending on the structure of amino group.

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Introduction

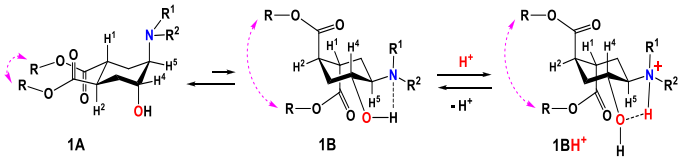
Mechanical or conformational molecular switches are molecular systems able to change the relative orientation of their parts under external stimulus. They play a central role in a design of controllable compounds, molecular machinery and intelligent materials with a variety of possible applications including drug release, new sensor techniques or information storage and transmission.[1-15] The cyclohexane-based molecular systems have been designed as an efficient type of such switches.[12-14] In particular, the *trans*-2-aminocyclohexanol moiety (Scheme 1) was used to construct the conformationally controlled crown-ethers and podands,[12] and the pH-sensitive 'flipids' for 'fliposomes'.[13,15-17] Protonation of the amino group in these compounds generates a strong intramolecular hydrogen bond of HO×××H-N$^+$ type (in **1B**·H$^+$ on Scheme 1). This bond stabilizes the originally unstable conformer **1B**, thus spreading the ester groups (counterbalances) at the other end of the molecule away from each other into axial positions ('peacock effect'[13]). The change of shape dramatically changes the ability of molecule to interact with other molecules or ions (depending on the nature of R), for example to pack into lipid bilayers. The variation of amino groups allows a broad tuning of the conformational equilibrium, and the basicity of amino functions could be adjusted for a conformational response within a selected range of pH.[13-18] Other cyclic and non-cyclic scaffolds, and more complex molecular devices were also suggested recently as pH-sensitive conformational switches for similar applications.[1-15,18,19]

To further expand the variety of potential pH-triggers, we synthesized and explored similar structures **2** based on *trans*-1,2-bis(benzoyloxy)cyclohexane, where benzoyloxy groups (PhCOO-) play the role of counterbalances (Scheme 2). The model compounds **2a-c** containing benzoyloxy groups, the amino and hydroxyl substituents were synthesized according to Scheme 3. Similar to previous studies,[13-18] the diastereomers **2** with the required relative configuration of substituents were the only isolable products because of the stereospecific epoxide cleavage. The conformational behavior of the cyclohexane derivatives **2a-c** was evaluated in various conditions by ^{1}H NMR spectroscopy (Table 1).

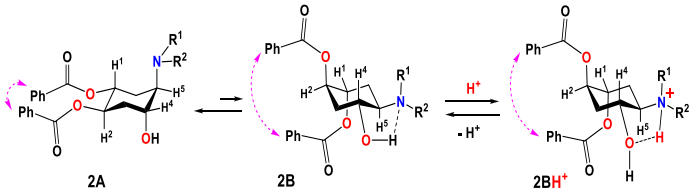
Experimental

The chemicals used in this study were purchased from commercial sources (Alfa Aesar, Sigma-Aldrich, TCI) and used without additional purification. All solvents were purified by conventional techniques prior to use. Column chromatography was performed on silica gel (40-75 μm, Sorbent Technologies). The reactions were monitored by TLC on silica gel 2.5 × 7.5 cm plates, Analtech Inc (eluent hexane:EtOAc; visualization by UV and staining with phosphomolybdic acid, PMA).

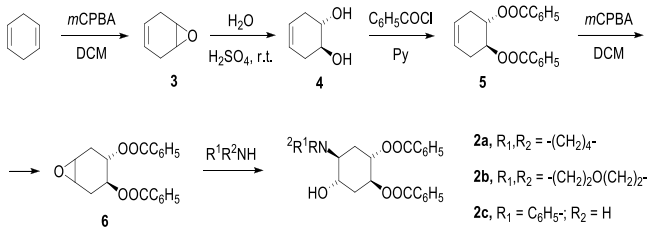
^{1}H NMR and ^{13}C NMR spectra were acquired on JEOL ECA-600 NMR spectrometer (600 MHz for ^{1}H and 150 MHz for ^{13}C)



Scheme 1. Acid-induced conformational switch in *trans*-2-aminocyclohexanols **1** with the alkoxycarbonyl groups (-COOR) as counterbalances.



Scheme 2. Acid-induced conformational switch in *trans*-2-aminocyclohexanols **2** with the benzoyloxy groups (PhCOO-) as counterbalances.



Scheme 3.

with spinning at rt. ^{1}H-^{1}H-COSY and ^{1}H-^{13}C-HMQC techniques were used to assign the signals.

^{1}H NMR titration experiments were used to observe a change of conformational equilibrium with a change of pH. Compounds **2a-c** were dissolved in CD_3OD (0.02-0.03 M), and the changes in chemical width and the chemical shifts of the protons geminal to the substituents were monitored by ^{1}H NMR spectra (600 MHz) during titration of the solution with *d*-trifluoroacetic acid (*d*-TFA). Acid was dissolved in CD_3OD (1 M) and added to a solution of compound **2** (0.6 mL) in small portions (0.5-5 μL). After every addition the solution was mixed thoroughly by gentle shaking, and its pH (pD) was measured using a combination pH micro electrode (8220BNWP, ThermoFisher Scientific). Shaking and measuring was repeated 3-4 times until a value of pD reading was constant. After recording the ^{1}H NMR spectrum, pD was measured again: the original and final values matched within 0.05 units. The spin-spin coupling constants between several pairs of vicinal protons attached to the cyclohexane moiety are strongly conformation-dependent, which allowed an assignment of a predominant conformation and an estimation of a position of the conformational equilibrium as described previously.[14-18]

trans-4,5-Cyclohexenediol ***4***

Cyclohexa-1,4-diene (9.70 mL, 102.5 mmol) was stirred in 400 mL of dichloromethane at 0°C, and *m*-CPBA (20.44 g, 118.5 mmol) was added in a portion-wise fashion during 1 h, followed by stirring at r.t. for 17 h. The mixture was quenched with 5% w/w aq. Na_2SO_3 (200 mL), followed by vigorous stirring for 1 h. The water layer was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic extracts were washed with sat. $NaHCO_3$ (3 x 100 mL) and brine (2 x 75 mL), carefully concentrated through vacuum distillation to remove as much CH_2Cl_2 as possible without distilling off epoxide **3**. To produce the diol **4,** 200 mL of deionized water was added to the solution of epoxide **3** followed by 2.6 mL of 10% H_2SO_4 and left to stir at r.t. for 24 h. After the starting epoxide was consumed (TLC; hexane:EtOAc, 1:1), the reaction mixture was neutralized with sat. $NaHCO_3$ until pH 5-6, then extracted with EtOAc (1 x 100 mL, followed by 4 x 50 mL) until no diol was present in the aqueous phase. The combined extracts were dried over anhydr. Na_2SO_4 and concentrated on a rotary evaporator resulting in white solid **4**: yield 7.60 g (65%). ^{1}H NMR ($CDCl_3$): δ 2.07 (m, 2H; H^{3a}+H^{6a}), 2.48 (m, 2H; H^{3e}+H^{6e}), 3.10 (br.s., 2H; OH), 3.70 (m, 2H; H^1+H^2), 5.53 (m, 2H; H^4+H^5). ^{13}C NMR ($CDCl_3$): δ 33.5 (C^3+C^6), 72.3 (C^1+C^2), 124.6 (C^4+C^5).

Cyclohexene-4,5-diyl dibenzoate ***5***

Diol **4** (1.88 g, 16.45 mmol) and benzoyl chloride (5.60 mL, 5.10 mmol) were stirred in 10 mL of pyridine at 0ºC under argon for 1 h, then left to stir at r.t. for 72 h monitored by TLC (hexane:EtOAc, 1:1). The reaction was quenched with 20 mL of water and slowly stirred for 30 min. The precipitate was filtered off and washed with 0.5 M $NaHCO_3$ (3 x 10 mL) and subsequently recrystallized from ethanol to yield1.96 g (37%) of **5** as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.40 (dt, 2H; H^{3a}+H^{6a}), 2.79 (d, 2H; H^{3e}+H^{6e}), 5.51 (m, 2H; H^4+H^5), 5.68 (m, 2H; H^1+H^2), 7.37 (t, 4H; Ph), 7.50 (td, 2H; Ph), 7.97 (d, 4H; Ph). ^{13}C NMR ($CDCl_3$): δ 30.3 (C^3+C^6), 70.8 (C^4+C^5), 123.9 (C^1+C^2), 128.4 (Ph), 129.7 (Ph), 133.1 (Ph), 166.1 (C=O).

(3S,4S)-7-oxabicyclo[4.1.0]heptane-3,4-diyl dibenzoate **6**

Dibenzoate **5** (1.73 g, 5.37 mmol) was dissolved in 250 mL of dry CH_2Cl_2, and *m*-CPBA (8.59 g, 49.78 mmol) was slowly added at 0ºC in a portion-wise fashion during 1 h, followed by stirring at r.t. for 32 h. After the diol **4** was fully consumed (TLC; hexane:EtOAc, 4:1) the reaction mixture was washed with 5% Na_2SO_3 (75 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic extracts were washed with sat. $NaHCO_3$ (2 x 50 mL) and brine (3 x 15 mL), then dried over anhydr. Na_2SO_4 and concentrated on a rotary evaporator. The residue was purified by column chromatography (silica gel, hexane:EtOAc, 4:1) to yield a white solid **6**: 1.15 g (80%). ^{1}H NMR ($CDCl_3$): δ 2.11 (m, 1H; H^{3a}), 2.24 (m, 1H; H^{6e}), 2.75 (m, 1H; H^{6a}), 2.82 (m, 1H; H^{3e}), 3.25 (t, 1H; H^5). 3.36 (m, 1H; H^4), 5.26 (m, 1H; H^1), 5.47 (m, 1H; H^2), 7.35 (t, 4H; Ph), 7.48 (m, 2H; Ph), 7.93 (m, 4H; Ph). ^{13}C NMR ($CDCl_3$): δ 29.5 (C^3+C^6), 50.1 (C^5), 52.8 (C^4), 128.4 (Ph), 129.7 (Ph), 133.2 (Ph), 165.7 (C=O), 166.1 (C=O).

(1S,2S,4S,5S)-4-hydroxy-5-(pyrrolidin-1-yl)cyclohexane-1,2-diyl dibenzoate ***2a***

Epoxide **6** (255 mg, 0.75 mmol) and an excess of pyrrolidine (375 mg, 5.28 mmol) were stirred in 4 mL of *i*-PrOH:THF (1:1) at r.t. and for 8 days, until the complete consumption of epoxide **6** (TLC; hexane:EtOAc, 1:1). The residue was purified by column chromatography (silica gel; hexane:EtOAc, gradient washing 4:1→1:1) to yield **2a** (48 mg; 16%) as ivory crystals. ^{1}H NMR ($CDCl_3$): δ 1.82 (m, 4H; CH_2CH_2, pyrrolidinyl), 2.10 (m, 2H; H^{3a}+H^{6a}), 2.18 (dt, 1H; H^{6e}), 2.42 (dt, 1H; H^{3e}), 2.71 (m, 2H; CH_2N, pyrrolidinyl), 2.81 (m, 2H; CH_2N, pyrrolidinyl), 2.90 (t, 1H *J* = 9.3 Hz; H^5), 4.06 (td, *J* = 8.9, 3.8 Hz; H^4), 5.49 (m, 2H; H^1+H^2), 7.44 (q, 4H; Ph), 7.57 (m, 2H; Ph), 8.02 (m, 4H; Ph). ^{13}C NMR ($CDCl_3$): δ 23.5 ($\underline{C}H_2\underline{C}H_2$, pyrrolidinyl), 24.2 ($C^6$), 33.3 ($C^3$), 49.0 ($CH_2N$, pyrrolidinyl), 61.6 ($C^5$), 66.8 ($C^4$), 70.3 ($C^1$+$C^2$), 128.6 (Ph), 129.7 (Ph), 133.2 (Ph), 165.2 (C=O), 165.3 (C=O).

(1S,2S,4S,5S)-4-hydroxy-5-morpholinocyclohexane-1,2-diyl dibenzoate ***2b***

Epoxide **6** (250 mg, 0.74 mmol) and morpholine (214 mg, 2.46 mmol) were dissolved in 3 mL of *i*-PrOH:THF:H_2O (1:1:1), and left to stir at r.t. for 48 h until the complete consumption of the epoxide (TLC; hexane:EtOAc, 1:1). The residue was purified by column chromatography (silica gel; hexane:EtOAc, gradient washing 4:1→1:1) to yield **2b** (88 mg; 28%) as a yellow-red paste. ^{1}H NMR ($CDCl_3$): δ 1.95 (m, 1H; H^{6a}), 2.05 (m, 1H; H^{3a}), 2.22 (dt, 1H; H^{6e}), 2.52 (m, 3H; H^{3e}+CH_2N, morpholyl), 2.80 (m, 3H; H^5+CH_2N, morpholyl), 3.76 (m, 4H; CH_2O morpholyl), 3.99 (td, *J* = 10.5, 4.4 Hz; H^4), 4.33 (br.s., 2H; OH, NH), 5.40 (q, *J* = 3.2 Hz; H^2), 5.47 (q, *J* = 3.3 Hz; H^1), 7.47 (m, 4H; Ph), 7.60 (m, 2H; Ph), 8.03 (m, 4H; Ph). ^{13}C NMR ($CDCl_3$): δ 23.1 (C^6), 33.3 (C^3), 49.0 (CH_2N, morpholyl), 64.10 (C^4), 64.9 (C^5), 67.3 (CH_2O, morpholyl), 69.8 (C^1+C^2), 128.7 (Ph), 129.8 (Ph), 133.5 (Ph), 165.0 (C=O).

(1S,2S,4S,5S)-4-hydroxy-5-(phenylamino)cyclohexane-1,2-diyl dibenzoate ***2c***

Epoxide **6** (258 mg, 0.76 mmol) and aniline (629 mg, 8.84 mmol) were stirred in 2 mL of THF for 12 weeks at 60°C until the complete consumption of the epoxide (TLC; hexane:EtOAc,

4:1). The reaction mixture was concentrated on a rotary evaporator and purified by column chromatography (silica gel, hexane-EtOAc, gradient washing 12:1→1:1) yielding **2c** (200 mg; 61%) as white-brown crystals that turned into dark purple once completely dry. ^{1}H NMR: δ 1.94 (m, 1H; H^{6a}), 2.22 (m, 1H; H^{3a}), 2.43 (m, 1H; H^{3e}), 2.49 (m, 1H; H^{6e}), 3.76 (td, *J* = 9.1, 4.0 Hz; H^5), 3.78 (br.s., 2H; OH, NH), 4.02 (td, *J* = 9.0, 4.0 Hz; H^4), 5.47 (q, *J* = 4.1 Hz; H^1), 5.51 (q, *J* = 4.2 Hz; H^2), 6.73 (m, 3H; C_6H_5N), 7.16 (t, 2H; C_6H_5N), 7.44 (t, 2H; C_6H_5), 7.47 (t, 2H, C_6H_5), 7.59 (m, 2H; C_6H_5), 8.03 (d, 2H; C_6H_5), 8.08 (d, 2H; C_6H_5). ^{13}C NMR ($CDCl_3$): δ 31.1 (C^6), 33.4 (C^3), 54.8 (C^5), 69.6 (C^4), 70.0 (C^1), 70.3 (C^2), 114.0 (C_6H_5N), 118.7 (C_6H_5N), 128.6 (Ph), 128.7 (Ph), 129.6 (C_6H_5N), 129.8 (Ph), 133.5 (Ph), 147.2 (C_6H_5N), 165.29, 165.35 (C=O).

Results and Discussion

We examined the fast equilibrium [**2A**] ⇄ [**2B**] ⇄ [**2B**·H$^+$] (Scheme 2) 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 an assignment of a predominant conformation and an evaluation of the position of conformational equilibrium: 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.[20,21] 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 [14-18] using the Eliel equation [21,22] applied to the averaged signal width $W = \Sigma J_{HH}$ (a sum of spin-spin couplings) of the protons H^4 geminal to the hydroxy group (Scheme 2): $W_{observed} = W_A \cdot n_A + W_B \cdot n_B$.[20] The H^4 signals were well resolved and had chemical shifts in a region apart from the signals of other coupled protons. The parameter *W* was measured as a distance between the terminal peaks of a multiplet (Figure 1, Table 1). The evaluated share of conformer **2B** (n_B) thus includes both the non-protonated form **2B** and the protonated form **2B**·H$^+$ (Scheme 2). The limiting parameter W_B was obtained from the H^4 signal width for the strongly acidic solutions of **2a-c** where the equilibria were completely shifted to conformers **2B** (Table 1). The limiting parameter W_A was assumed to equal 9 Hz based on the reported data for the related cyclohexane derivatives with completely biased conformational equilibrium.[14,18] The coupling constants for other protons of the cycle were used when possible to confirm the conformational assignments. We did not use the averaged chemical shifts for the equilibrium estimations because of their narrow range of variation and general sensitivity to the nature of solvent, temperature, additives, etc.

We found that the conformational equilibria for molecules **2a-c** strongly depend on the solvent. The conformer **2B** is more stable in the non-polar $CDCl_3$ (74-97%) than in polar CD_3OD (15-51%). Similar solvent dependence was previously found for other *trans*-2-aminocyclohexanols.[14-18] A plausible explanation may be an intramolecular hydrogen bond OH···N and/or electrostatic attraction between substituents, which stabilize **2B** in $CDCl_3$, but are interrupted in *d*-methanol and replaced by the similar intermolecular interactions with CD_3OD.

To explore the possible acid-induced shift of the conformational equilibrium due to the intramolecular hydrogen bond of O···H-N$^+$ type and enhanced polar interactions, we titrated the solutions of compounds **2a-c** in CD_3OD with *d*-trifluoroacetic acid (Figure 2). During addition of *d*-TFA, the peak widths *W* (the sum of spin-spin couplings) increased for protons H^4 and H^5 and decreased for protons H^1 and H^2 indicating a shift of equilibrium towards **2B**. *d*-TFA was added to a sample until the peak width for H^1, H^2, H^4, and H^5 did not change anymore (up to a 10-20-fold excess of *d*-TFA, down to apparent pD ≈ 0.5-2). Thus a strong shift of equilibrium towards the form **2B**D$^+$ was observed (Scheme 2, Table 1), especially for the pyrrolidinyl-derivative **2a** (15 → 100%), which was the most sensitive to acid. We believe the equilibrium is completely biased

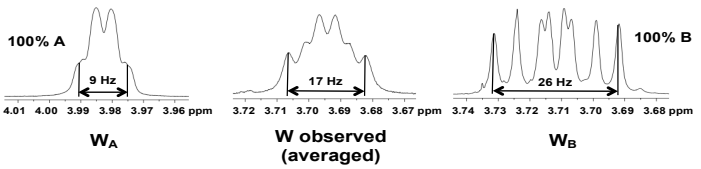


Figure 1. Dependence of the signal width $W = \Sigma J_{HH}$ for H^4 on the position of conformational equilibrium (Scheme 2)

Table 1. ^{1}H NMR data and conformational parameters.[a)]

Compound, solvent, acid	*H4*		*H5*		*H1*		*H2*		n_B (n_{BH+}), %	ΔG_{B-A}, kJ/mol
	δ	*W, Hz*	δ	*W, Hz*	δ	*W, Hz*	δ	*W, Hz*		
2a in $CDCl_3$	4.06	21.3	2.90	18.5 [b)]	5.49	[c)]	5.49	[c)]	74	-2.6
2a in CD_3OD	4.18	11.5	2.52	15.8 [d)]	5.50	23.4	5.62	23.9	15	4.3
+ CF_3COOD [e)]	4.16	25.6 [f)]	3.65	[c)]	5.48	10.0	5.40	9.6	~100	≤ -10
2b in $CDCl_3$	3.99	25.6	2.80	[c)]	5.47	~10 [b)]	5.40	~10 [b)]	97	-8.6
2b in CD_3OD	4.16	17.7	2.63	[c)]	5.37	17.4	5.49	17.7	51	-0.1
+ CF_3COOD [e)]	4.30	26.2 [f)]	3.58	[c)]	5.49	10.5	5.38	10.1 [b)]	~100	≤ -10
2c in $CDCl_3$	4.02	22.1	3.76	22.3 [c)]	5.47	12.3	5.51	12.4	77	-3.0
2c in CD_3OD	4.04	16.5	3.71	16.9	5.51	18.5	5.55	18.3	44	0.6
+ CF_3COOD [e)]	4.13	26.1 [f)]	3.77	26.9	5.37	9.7 [b)]	5.39	9.4 [b)]	~100	≤ -10

a) 600 MHz; 0.02-0.03 M solutions; 298K;
b) poorly resolved;
c) partially or completely overlapped with other signals;
d) very poorly resolved; width at ½ of height;
e) *d*-trifluoroacetic acid was added in large excess (x10-20) to CD_3OD solution;
f) limiting parameters W_B.

towards the form **2B** in these conditions. Therefore, the values *W* observed in excess acid (Table 1) can be used as the limiting parameters W_B.

The NMR titration curves for the signal widths (Figure 2) demonstrated that the studied model *trans*-2-aminocyclohexanols **2a-c** did not change their relative conformer population gradually over the whole course of incremental addition of *d*-TFA, but did so only within a narrow range of acidity (~3 units pD): between pD 8.5 and 6 for pyrrolidinyl-derivative **2a**, between pD 6.5 and 3.5 for morpholyl-derivative **2b**, and between pD 3.5 and 1 for phenylamino-derivative **2c**. This observation indicated that the variation of substituents at amino group allows a tuning of the pH-sensitivity for the aminocyclohexanol-based molecular switches. The relative position of these transitional areas (buffer zones) matches in general an expectation of a higher basicity for pyrrolidinyl group as compared to morpholyl group, and the lower basicity for the phenylamino group. Using the method based on Henderson-Hasselbalch equation,[23] we estimated the pK_a values for the protonated compounds **2**·D^+ in CD_3OD solutions as an apparent pD at the halfway point in the central part of their NMR-titration curves: pK_a = 7.4 (**2a**), 4.9 (**2b**), 2.5 (**2c**). The basicity of compounds **2a-c** practically coincided with the basicity of previously studied cyclohexanols **1a-c** with the same set of amino groups as in the current research but with two EtOOC-groups as the conformational counterbalances: pK_a = 7.6 (**1a**), 4.9 (**1b**), 2.6 (**1c**).[14] Apparently, the nature of remote substituents at C^1 and C^2 does not affect the basicity of the studied models.

At the same time, the difference of counterbalances does affect the conformational equilibria. The conformers **2B** (Scheme 2, Table 1) are generally more populated than the conformers **1B** (Scheme 1).[14] This indicates a weaker preference of PhCOO-groups in **2** for equatorial position (in the form **2A**) than the equatorial preference of EtOOC-groups in **1**. Comparing the values of $\Delta G_{B\text{-}A}$ for **1**[14] and **2**, we can estimate this difference as 2.5-4 kJ/mol in methanol solutions (without acid). It is smaller than the difference of 5-6 kJ/mol that could be predicted from the A- values of these groups (2.1 kJ/mol for PhCOO and 4.5-5 kJ/mol for EtOOC[21]). Thus, a variation of the counterbalancing groups allows a broader tuning of the conformational equilibrium of these compounds, which can be used as conformational pH-triggers.

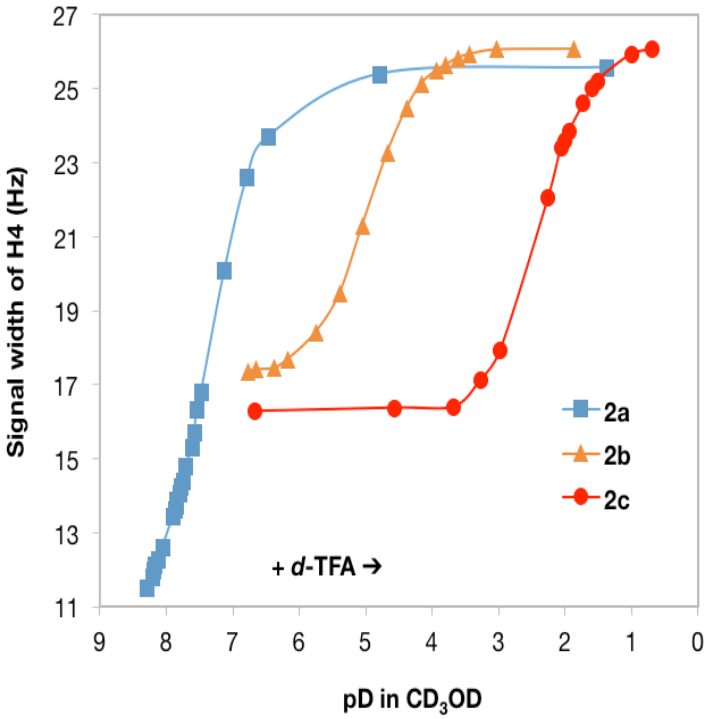


Figure 2. Dependence of the signal width (*W*) on pD for the protons H^4 measured for the CD_3OD solutions of compounds **2a-c**.

Acknowledgements

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