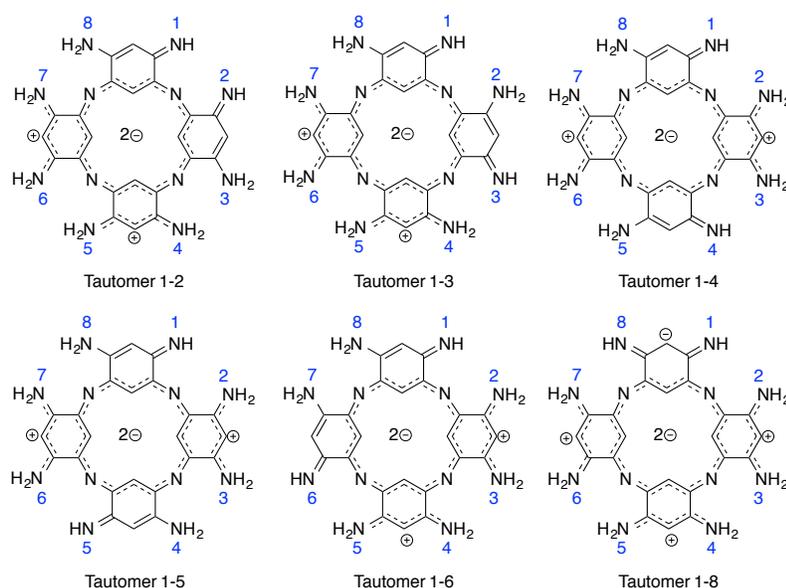


Understanding the unconventional tautomerism in azacalixpyrins[†]: Electronic supporting information

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S1 Representation of the different tautomers



Scheme S1 Representation of the different tautomers of **1** in one of their limit Lewis structures.

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S2 Optical spectra and aromaticity

Table S1 Vertical $S_1 \leftarrow S_0$ excitation energy, ΔE , in eV, and oscillator strength, f , for the different tautomers. See caption of Table 2 in the main text for more details.

Method	$\Delta E/\text{eV}$					
	1-2	1-3	1-4	1-5	1-6	1-8
Gas (M06-2X)	1.56	1.47	1.45	1.31	1.55	0.72
Water (PCM-B3LYP)	1.52	1.45	1.40	1.33	1.50	0.66
Method	f					
	1-2	1-3	1-4	1-5	1-6	1-8
Gas (M06-2X)	0.16	0.11	0.24	0.19	0.17	0.08
Water (PCM-B3LYP)	0.12	0.09	0.22	0.15	0.15	0.06

Table S2 NICS(0), in ppm, at the centre of the macrocycle.

Method	NICS/ppm					
	1-2	1-3	1-4	1-5	1-6	1-8
Gas (M06-2X)	-3.6	-4.1	-5.7	-7.8	-4.6	-2.8
Water (PCM-B3LYP)	-5.2	-5.3	-6.5	-7.6	-6.1	-6.2

Table S3 NICS(1), in ppm, determined at the PCM(water)-B3LYP level of theory.

NICS/ppm					
1-2	1-3	1-4	1-5	1-6	1-8
-5.2	-5.2	-6.4	-7.4	-6.0	-6.5

S3 NMR spectra for **1**

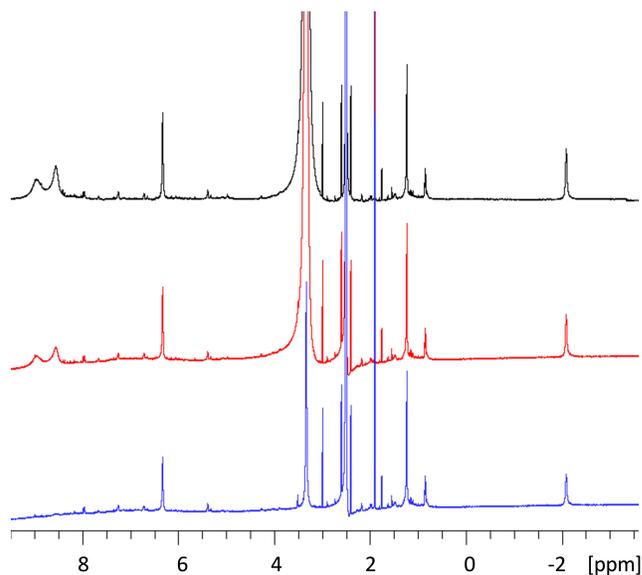


Fig. S1 ^1H NMR spectrum and signal integrations of **1** in $\text{DMSO-}d_6$ with traces of H_2O . The residual protonated DMSO ($\text{DMSO-}d_5$) and water signals are truncated. Experiments performed with presaturation of the water peak at 1×10^{-8} W (red) and 1×10^{-6} W (blue) are compared to the spectrum recorded without presaturation (black). Spectra were recorded at 700 MHz and 303 K with a cryogenic probe (see Methods). As observed for the protonated molecule $\mathbf{1.H}_2^{++}$, the NH_2 signal of **1** is considerably attenuated upon presaturation due to the effect of chemical exchange with water, while the other signals are much less affected. The slight intensity decrease of some signals can be attributed to the cross-relaxation arising from dipolar interactions (see explanations in the body of the text).

S4 Representation of the transition states

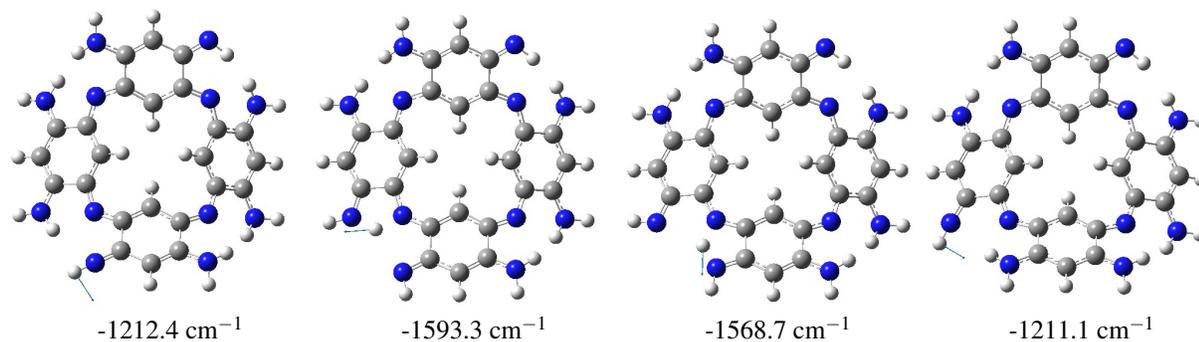


Fig. S2 Geometries of the transition states in the intramolecular tautomerisation mechanism in **1** (the minima are shown in Fig. 4a in the main text). The arrows show the nuclear displacements along the vibrational mode with the imaginary frequency (in cm^{-1}).

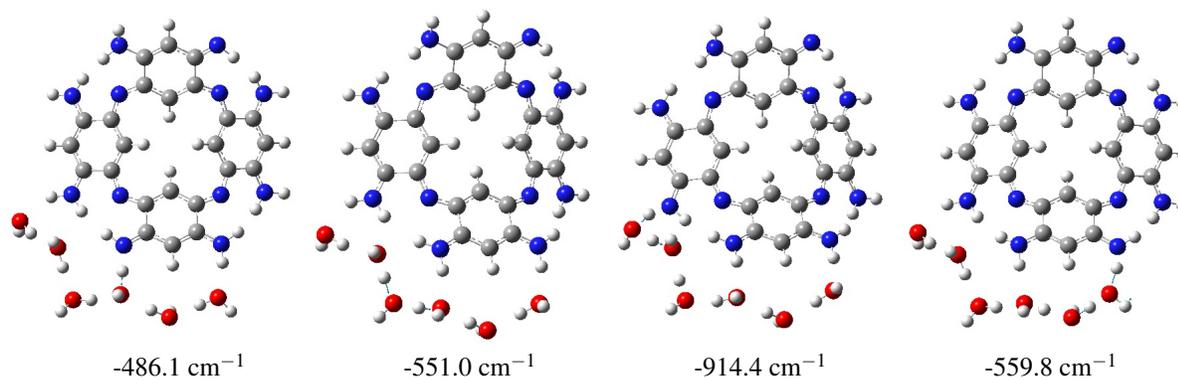


Fig. S3 Geometries of the transition states in the water-mediated tautomerisation mechanism in **1** (the minima are shown in Fig. 4b, main text).

S5 Methodological impact (reaction paths of 1)

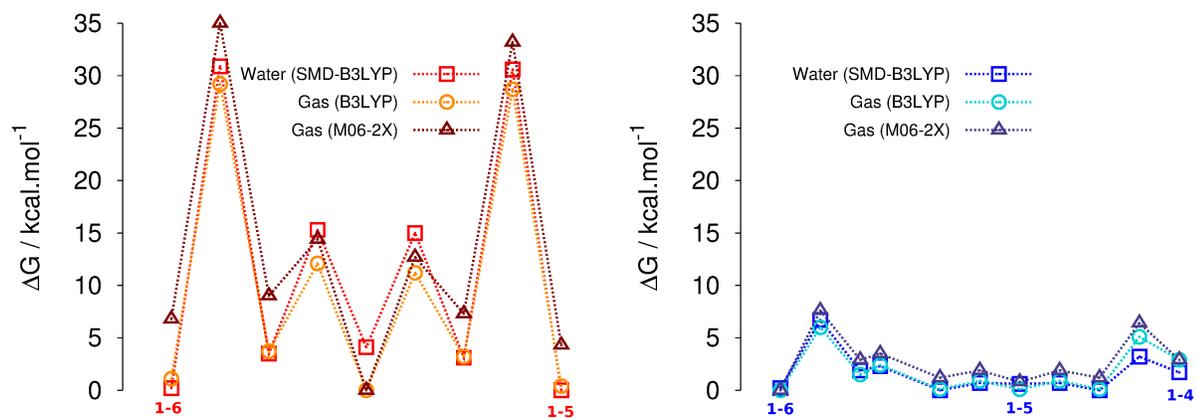


Fig. S4 Energies of the geometries of the minima and transition states in the intramolecular (left) and water-assisted (right) tautomerisation mechanisms, using the B3LYP or M06-2X DFT functionals, in gas phase and with the SMD (water) continuum solvation model.

S6 Rotation of NH in **1** in the presence of explicit water molecules.

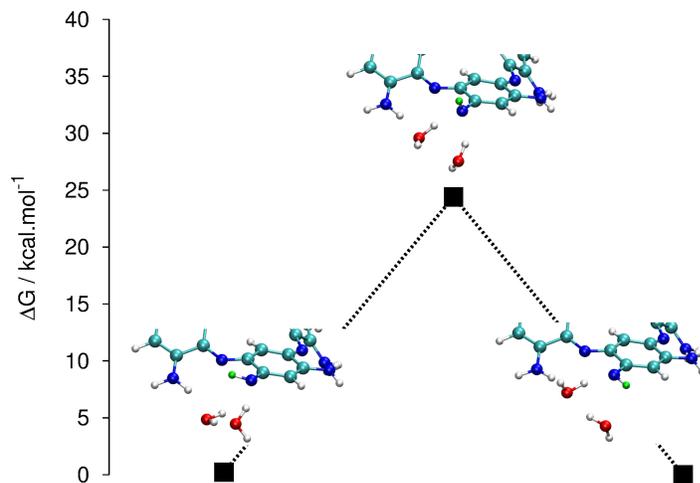


Fig. S5 Energies of the geometries of the minima and transition states obtained for the rotation of the imine (rate limiting step for the intramolecular tautomerism in **1**) in the presence of two explicit water molecules. Results at the SMD(water)-B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) level. Only the relevant part of the molecule is displayed for clarity.

S7 Water-assisted process: two shells of explicit water molecules

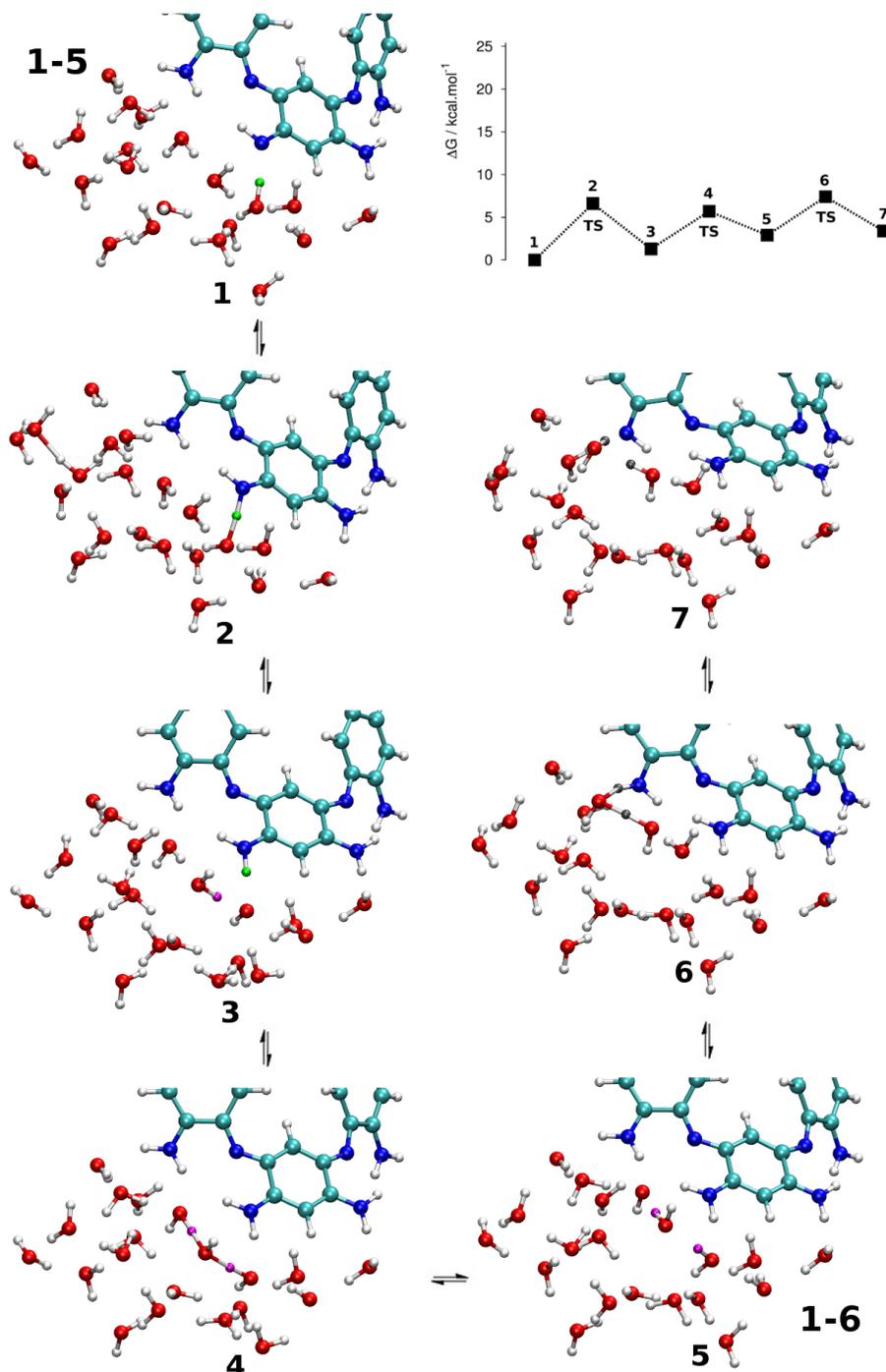


Fig. S6 Water-assisted 1-5 \rightleftharpoons 1-6 tautomerisation pathway of **1** with 20 surrounding water molecules. Results obtained at the SMD(water)-B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) level.

S8 Determination of the pK_a s of $1.H_2^{++}$ in DMSO/H₂O (80/20 v/v).

Distilled water was further purified by passing through a mixed bed of ion-exchanger (Bioblock Scientific R3-83002, M3-83006) and activated carbon (Bioblock Scientific ORC-83005). The distilled water and spectroscopic grade DMSO (Sigma, > 99.9%) were de-oxygenated using CO₂- and O₂-free argon prior to use (Sigma Oxiclear cartridge). The stock solutions were prepared by weighing the solid product using a Mettler Toledo XA Dual Range balance (precision 0.01 mg). The complete dissolution of $1.H_2^{++}$ (chloride salt) in pure DMSO was achieved with the help of an ultrasonic bath. All physicochemical measurements were carried out at 25.0 ± 0.2 °C.

2.5 mL of a stock solution of $1.H_2^{++}$ in DMSO (4.42×10^{-4} M) were added to 40 mL of DMSO/water (80/20 v/v) containing 0.1 M NaClO₄ (NaClO₄.H₂O, Merck, p.a.; as supporting electrolyte for maintaining the ionic strength) in a jacketed cell (Metrohm) maintained at 25.0 ± 0.2 °C. The free hydrogen ion concentration was measured with a combined glass electrode (Metrohm 6.0234.500, Long Life) and an automatic titrator system 794 Basic Titrino (Metrohm). The Ag/AgCl reference glass electrode was filled with 0.1 M DMSO/water (80:20 v/v) solution of NaClO₄ (Fluka, p.a.) and calibrated as a hydrogen concentration probe by titrating known amounts of freshly prepared perchloric acid ($\sim 10^{-1}$ M from HClO₄, PROLABO, normapur, 70% min) with CO₂-free sodium hydroxide solution ($\sim 10^{-1}$ M from NaOH, BDH, AnalaR) prepared as well in DMSO/water (80:20 v/v).¹ The GLEE program was applied for the glass electrode calibration and to check carbonate levels of the NaOH solutions used (< 5%). The autodissociation constant pK_w of the solvent was taken as 18.35.² The initial pH of the $1.H_2^{++}$ solution (2.47×10^{-5} M) was adjusted to ~ 2.5 with HClO₄, and the absorption spectrophotometric titrations versus pH ($\sim 2.5 < \text{pH} < \sim 17$) were carried out by addition of known volumes of NaOH solutions using the automatic titrator of the 794 Basic Titrino device. After each addition, an absorption spectra was repeatedly recorded using a Varian CARY 50 spectrophotometer fitted with Hellma optical fibers (Hellma, 041.002-UV) and an immersion probe made of quartz suprazil (Hellma, 661.500-QX) and interfaced (Cetrib) with the potentiometric unit. The absorption *versus* pH titration of $1.H_2^{++}$ was duplicated, and a good agreement between the pK_a values determined (see below).

The statistical processing of the spectrophotometric and potentiometric data sets was done with the Specfit program³⁻⁵ which adjusts the absorptivities and the stability constants of the species formed at equilibrium. Specfit uses factor analysis to reduce the absorbance matrix and to extract the eigenvalues prior to the multiwavelength fit of the reduced data set according to the Marquardt algorithm.^{6,7} Two pK_a values were evidenced and are given below (the value in parentheses correspond to the duplicated titration).

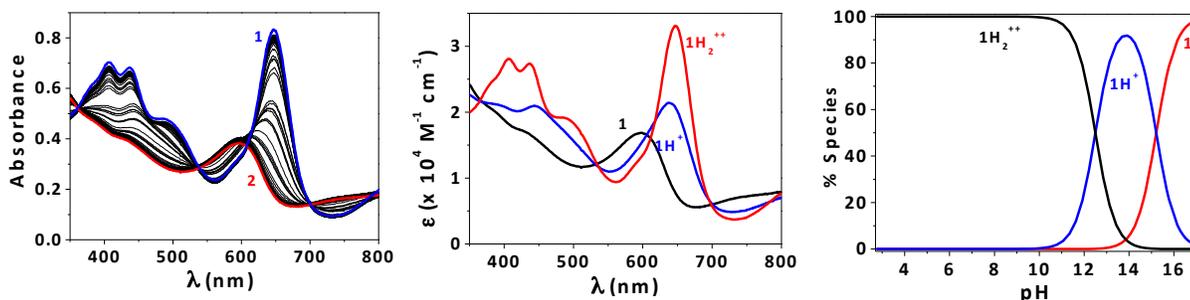
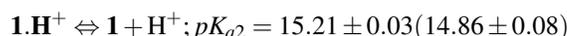
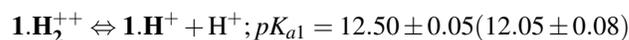


Fig. S7 Left: UV-Vis. absorption spectrophotometric titration of the azacalixphyrin $1.H_2^{++}$ (chloride salt) as a function of pH. Solvent: DMSO/water (80:20 v/v); $I = 0.1$ M (NaClO₄); $T = 25.0(1)$ °C; $[1.H_2^{++}]_0 = 2.47 \times 10^{-5}$ M; (1) pH = 2.70; (2) pH = 16.79. The absorption spectra are not corrected from dilution effects. Centre: Absorption electronic spectra of the azacalixphyrin **1** and its protonated species $1.H^+$ and $1.H_2^{++}$. Solvent: DMSO/water (80:20 v/v); $I = 0.1$ M (NaClO₄); $T = 25.0(1)$ °C. Right: Distribution diagrams of the protonated species of the azacalixphyrin **1** as a function of pH. Solvent: DMSO/water (80:20 v/v); $I = 0.1$ M (NaClO₄); $T = 25.0(1)$ °C.

S9 Rotation of the NH₂ in 1

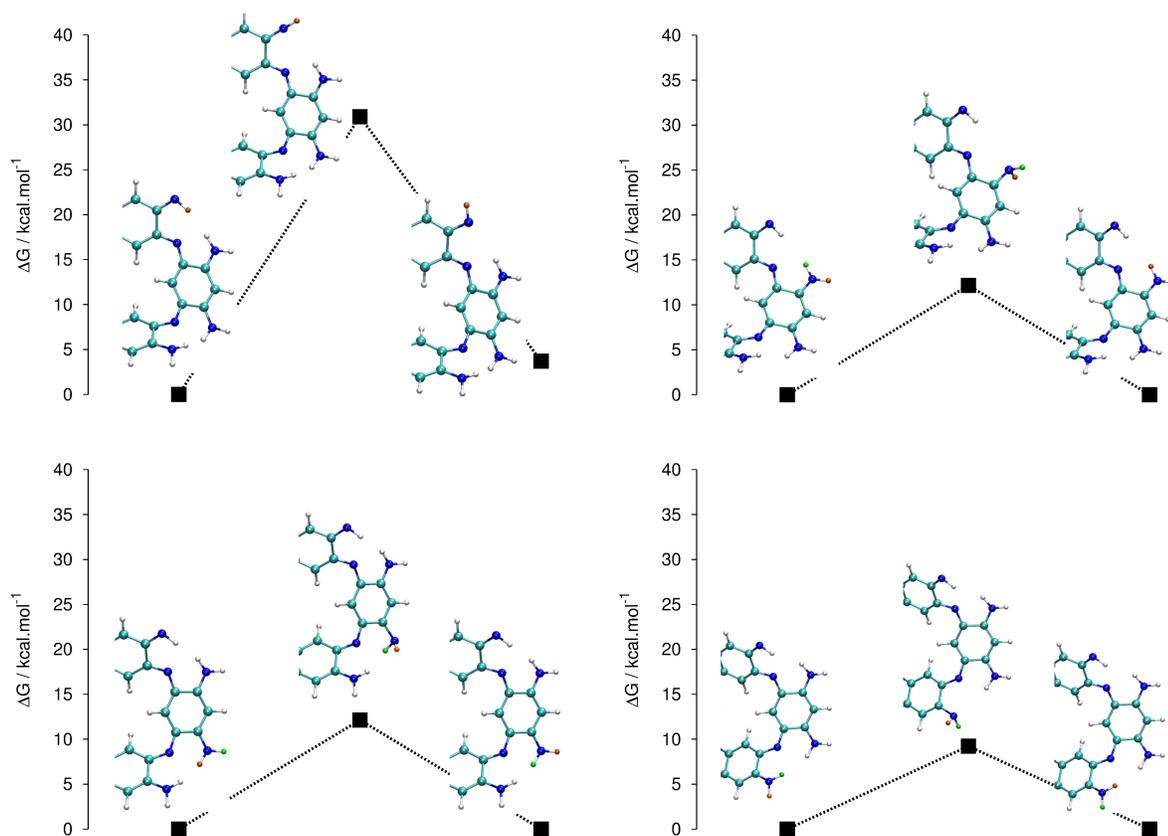


Fig. S8 Energy profiles for the rotation of non-equivalent NH₂ (and NH) in **1**. All results at the SMD(water)-B3LYP/6-311++G(d,p)//B3LYP/6-31G(d) level.

S10 Chemical exchange in $1.H_2^{++}$

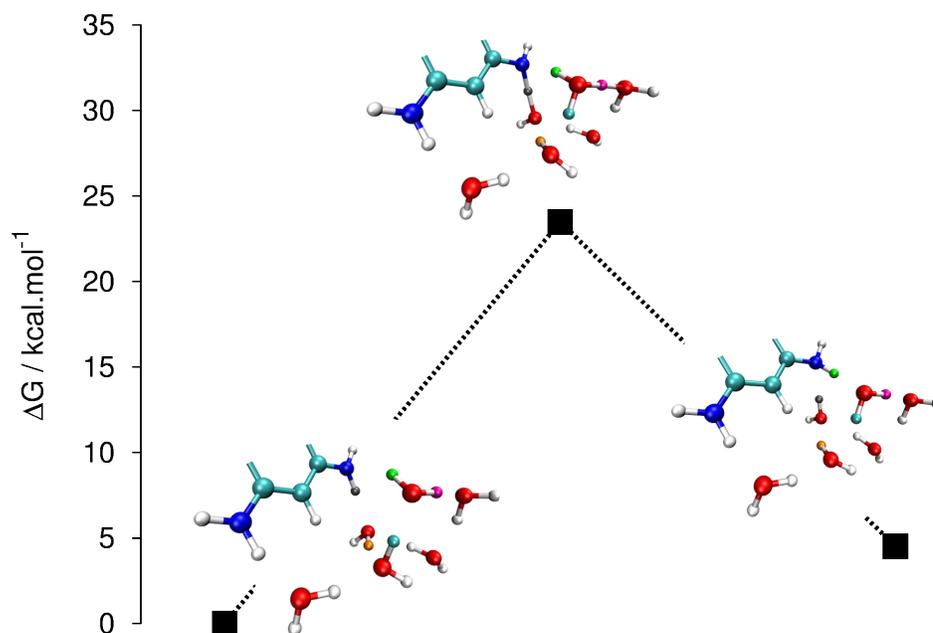


Fig. S9 Energy profile for the exchange of proton in one amine/iminium function of $1.H_2^{++}$. The starting and final macrocycle have the same protonation state, but one proton has been exchanged (brown/green) with the surrounding solvent molecules. For clarity, only the relevant part of the molecule is displayed. All results obtained at the SMD(water)-B3LYP level.

S11 Reaction profile for H-exchange with CH

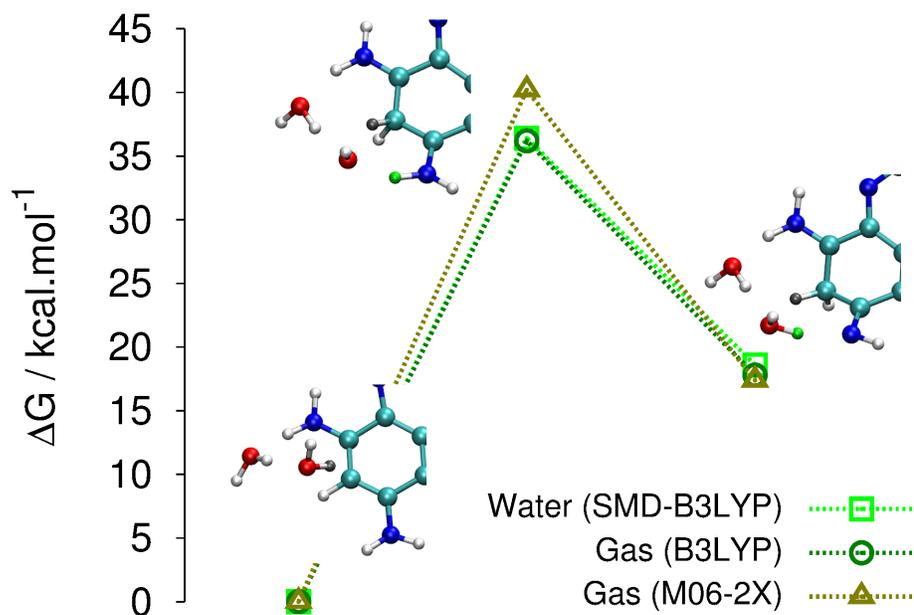


Fig. S10 Geometries and energies of the minima and transition state for the passage from a non-protonated CH group located in between two NH_2 (left) to a protonated CH_2^+ group located in between one NH_2 and one NH (right).

References

- 1 P. Gans and B. O'Sullivan, *Talanta*, 2000, **51**, 33–37.
- 2 R. Salvio, A. Casnati, L. Mandolini, F. Sansone and R. Ungaro, *Org. Biomol. Chem.*, 2012, **10**, 8941–8943.
- 3 H. Gampp, M. Maeder, C. J. Meyer and A. D. Zuberbühler, *Talanta*, 1985, **32**, 95–101.
- 4 H. Gampp, M. Maeder, C. J. Meyer and A. D. Zuberbühler, *Talanta*, 1985, **32**, 257–264.
- 5 H. Gampp, M. Maeder, C. J. Meyer and A. D. Zuberbühler, *Talanta*, 1986, **33**, 943–951.
- 6 D. W. Marquardt, *J. Soc. Ind. Appl. Math.*, 1963, **11**, 431–441.
- 7 M. Maeder and A. D. Zuberbuehler, *Anal. Chem.*, 1990, **62**, 2220–2224.