Cooperative Effects in Aminothiols: Acid-Base Equilibria and the Molecular Structure of 2-(*N*,*N*-Dimethylaminomethyl)thiophenol

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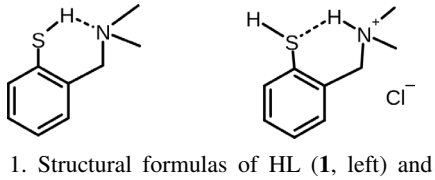
2-(*N*,*N*-Dimethylaminomethyl)thiophenol, (**1**, HL), is present as a non-zwitterionic aminothiol in the solid state, exhibiting an intramolecular S–H···N hydrogen bond. The S···N distances of the two independent molecules in the asymmetric unit are 2.929(10) and 3.050(10) Å. This structural feature is also present in an *ab initio* (MP2/6-31G*) optimized molecular structure. The investigation of the hydrogen bond by *ab initio* methods supports an n(N)-σ*(S–H) interaction as the reason for this bond type. On the basis of data from potentiometric acid-base titrations of a 0.01 M aqueous solution of $[H_2L]Cl$ with a 0.1 M aqueous solution of sodium hydroxide, values of 4.09 ± 0.01 and 11.50 ± 0.01 were obtained for pK_{a1} and pK_{a2} of $[H_2L]^+$. pK_{a1} is much smaller than pK_a of thiophenol while pK_{a2} is bigger than pK_a of benzyldimethylamine. The increased difference between pK_{a1} and pK_{a2} is attributed to the stabilization of HL by the intramolecular S–H···N hydrogen bond.

Key words: Single Crystal X-Ray Structure, *ab initio*, Hydrogen Bonds, Amino-thiophenols

Introduction

Hydrogen bonding plays an important role in various processes in chemical and biological systems. S–H···N and $^-$S···H–N$^+$ hydrogen bonds are of great significance in proteine chemistry. In a recent study, we could show that cysteamine is present as a zwitterionic tautomer, $^-SCH_2CH_2NH_3^+$, in the solid state [1]. Despite its tendency to chelate metal ions [2], intermolecular instead of intramolecular $^-$S···H–N$^+$ hydrogen bonds are present in the solid state of cysteamine. 2-(*N*,*N*-dimethylaminomethyl)thiophenol (**1**) is another well known metal-chelating N,S-ligand [3]. Due to the positions of the N and S atoms within the molecule, six-membered chelate rings are formed here (Scheme 1). In contrast to cysteamine, the donor atoms are sterically more shielded by their molecular environment. We were thus interested to study the molecular structure of and the hydrogen bonding in **1** (HL) and report here the findings of our investigations.



Scheme 1. Structural formulas of HL (**1**, left) and H_2L^+ (1·HCl, right).

Results and Discussion

Determination of pK_a values of H_2L^+

On the basis of data from potentiometric acid-base titrations of 50.0 mL of a 0.01 M aqueous solution of $[H_2L]Cl$ with a 0.1 M aqueous solution of sodium hydroxide, values of 4.09 ± 0.01 and 11.50 ± 0.01 were obtained for pK_{a1} and pK_{a2} of $[H_2L]^+$. The experimental data and the fitting curve are depicted in Fig. 1. pK_{a1} of $[H_2L]^+$ is much lower than pK_a of thiophenol (6.3) and pK_{a2} is significantly higher than pK_a of benzyldimethylamine (9.05) [4, 5]. This means that the difference between pK_{a1} und pK_{a2} is bigger than the pK_a difference between thiophenol and benzyldimethylamine. Obviously, the intramolecular proximity of the thiol and the amino group leads to a cooperative acid-base effect by which HL is stabilized against protonation as well as deprotonation. The stabilization of the proton is even bigger than in *N*,*N*-dimethylcysteamine (pK_{a2} = 11.1) for which

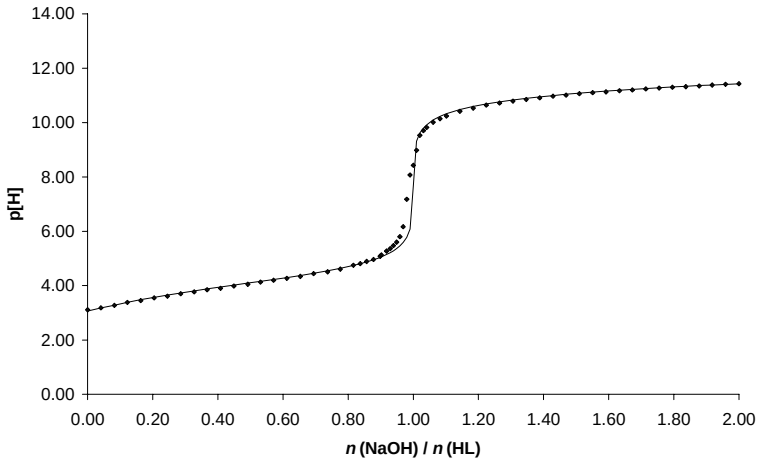


Fig. 1. p[H] curve of the potentiometric titration of $[H_2L]Cl$ with 0.100 M NaOH.

an intramolecular hydrogen bond in a five-membered ring has been proposed [6]. As a consequence, pK_{a1} and pK_{a2} cannot be attributed to protolysis of a distinct thiol or ammonium group. This cooperative effect found to operate in aqueous solution can be explained on the basis of the single crystal X-ray structure of HL.

Ab initio and single crystal X-ray structures

Most structural parameters of HL do not differ significantly in the two crystallographically different molecules found in the solid state (see Table 1). An exception is the distance S1···N1, which is of interest due to the intramolecular S−H···N hydrogen bond present in the molecule. The hydrogen bond is part of a six-membered ring, further involving two neighboring endocyclic carbon atoms of the aromatic ring and the exocyclic aliphatic carbon atom (see Fig. 2). Due

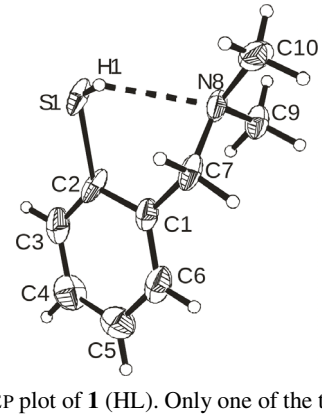


Fig. 2. ORTEP plot of **1** (HL). Only one of the two molecules present in the asymmetric unit is shown. Displacement ellipsoids are at the 50 % probability level.

Table 1. Selected structural data of **1** (HL) from single crystal XRD and *ab initio* MP2/6-31G(d) geometry optimization. Distances are given in Å, angles in degree[a].

	XRD (A)	XRD (B)	MP2 (**1A**)	MP2 (**1B**)
S1–C2	1.799(13)	1.767(10)	1.778	1.761
C2–C3	1.373(18)	1.366(17)	1.401	1.410
C3–C4	1.40(2)	1.388(16)	1.394	1.392
C4–C5	1.38(2)	1.41(2)	1.396	1.399
C5–C6	1.42(2)	1.37(2)	1.395	1.393
C6–C1	1.369(19)	1.391(15)	1.401	1.401
C1–C2	1.415(17)	1.436(18)	1.410	1.420
C1–C7	1.512(17)	1.496(17)	1.505	1.498
C7–N8	1.521(16)	1.515(13)	1.468	1.498
N8–C9	1.474(17)	1.496(15)	1.460	1.475
N8–C10	1.465(16)	1.486(16)	1.459	1.473
S1···N8	2.929(10)	3.050(10)	3.203	2.892
S1–C2–C1	121.1(10)	121.1(9)	122.2	122.3
Σ $(C–C–C)_{arom}$	719.8(31)	719.8(29)	720.0	720.0
Σ (C–N–C)	335.8(17)	334.1(16)	332.0	338.9
S1–H1···N8	116.6	108.1	139.5	154.7
S1–C2–C1–C7	8.3(17)	4.8(16)	−0.4	3.4
N8–C7–C1–C2	−50.8(15)	−55.7(15)	−63.5	−54.2
C9–N8–C7–C1	−59.2(13)	−56.2(13)	−62.9	−62.7

[a] A and B refer to the two crystallographically different molecules in the solid state structure of HL. **1A** and **1B** refer to the non-zwitterionic and the zwitterionic tautomer, respectively.

to ring strains, the deviation from a linear S–H···N arrangement is large.

In contrast to cysteamine, which exists as the zwitterionic tautomer $^{-}SCH_2CH_2NH_3^{+}$ in the solid state [1], HL is present as the non-zwitterionic tautomer. Among the 25 most intense peaks in a residual electron density map from the refinement of the single crystal X-ray data, there is none in a position which would suggest a zwitterionic form.

Ab initio investigations of HL (**1**) at the MP2 level have shown both, the non-zwitterionic form (**1A**), and

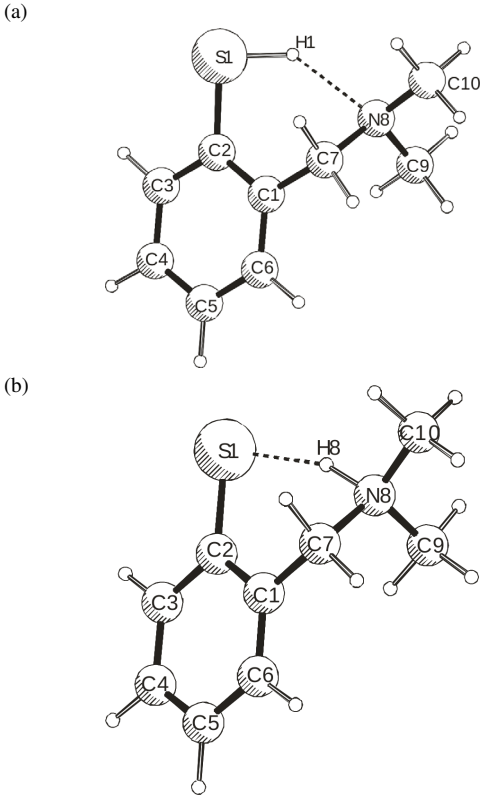


Fig. 3. (a) Plot of the non-zwitterionic tautomer **1A**, as obtained from MP2/6-31G* geometry optimization; (b) plot of the zwitterionic tautomer **1B**, as obtained from MP2/6-31G* geometry optimization.

the zwitterionic form (**1B**), to represent local minima on the potential energy surface (see Fig. 3). The free enthalpy of **1A** is calculated to be 25 kJ·mol^{-1} lower than that of **1B**.

Most *ab initio*-optimized geometrical parameters agree rather well with the data found in the solid state. In the present case, exceptions are the two parameters connected with the hydrogen bond, *i. e.* the S···N distance and the S–H···N angle. The *ab initio*-calculated S···N distance is much shorter in tautomer **1B** than in **1A**. Since ring conformations are quite similar in both tautomers, the smaller S···N distance in **1B** is attributed to an attractive Coulomb force between the $-S^-$ and $\equiv NH^+$ groups. The *ab initio*-obtained S–H···N angles for **1A** and **1B** are much wider than the average of the XRD values.

The S···H–N angle in the zwitterionic tautomer **1B** is much wider than its S–H···N analog in tautomer **1A** (see Table 1). An NBO analysis of the hydrogen bond revealed this to be due to an n(N)-σ*(S–H) interaction, the second order perturbation energy being calculated as 45 kJ·mol^{-1}. If the S–H bond vector is moved away from its minimum position where it is pointing towards the nitrogen lone pair, the energy of the molecule is substantially raised. This can be seen from a scan of the potential energy surface by a systematic variation of the torsion angle H1–S1–C2–C1 (see Fig. 4). The minimum at τ(H–S–C–C) = −33.1° corresponds to the optimized structure. For the second minimum, which is 9.3 kJ·mol^{-1} higher in energy, the torsion angle is 150.6°.

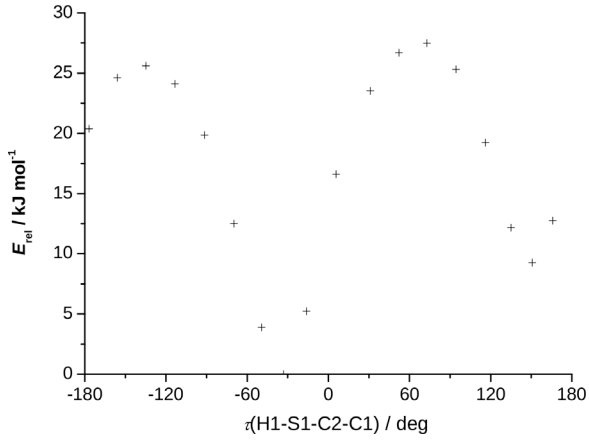


Fig. 4. Diagram showing the MP2/6-31G* potential energy of HL *vs*. the torsion angle H1–S1–C2–C1.

The conformations of the six-membered ring involving the hydrogen bond are also significantly different in the XRD and *ab initio* structures. In the solid state, the N···H hydrogen bond crosses an idealized plane defined by S1, C2, C1 and C7, while in the optimized *ab initio* structure, N8 and H1 are on the same side of this plane, forming a distorted boat.

Conclusion

2-(*N*,*N*-dimethylaminomethyl)thiophenol is stabilized by an intramolecular S–H···N hydrogen bond, leading to an increased difference between pK_{a1} and pK_{a2} as compared to pK_a of thiophenol and dimethylbenzylamine. Furthermore, knowledge of the pK_a values of aminothiols alone is not sufficient to predict whether or not the compounds are present as zwitterions in the solid state.

Experimental Section

Synthesis

2-(*N*,*N*-dimethylaminomethyl)thiophenol, (**1**, HL), was prepared according to a literature procedure [3]. Its identity

Table 2. Crystal structure data for HL[a].

Formula	$C_9H_{13}NS$
M_r	167.273
Cryst. size, mm^3	$0.032 \times 0.128 \times 0.256$
Crystal system	*Pba*2
Space group	orthorhombic
Temperature, K	173
a, Å	15.30(2)
b, Å	10.2445(2)
c, Å	6.5184(1)
V, Å^3	1830(3)
Z	8
$D_{calcd.}$, g cm^{-3}	1.215
Radiation; λ, Å	CuK_α; 1.54178
μ(CuK_α), cm^{-1}	26.1
F(000), e	720
hkl range	+19, +26, +6
$((\sin\theta)/\lambda)_{max}$, Å^{-1}	0.62
Refl. measured	3441 (incl. Friedel pairs)
Refl. unique	3261
R_σ	0.213
Param. refined	199
$R1(F)/wR2(F^2)$[a] (all reflections)	0.118 / 0.360
GooF[a]	1.003
$\Delta\rho_{fin}$ (max/min), e Å^{-3}	0.72 / −0.66

[a] $R1(F) = \Sigma\|F_o| - |F_c\|/\Sigma|F_o|$, $wR2(F^2) = \{\Sigma[w(F_o^2 - F_c^2)^2] / \Sigma[w(F_o^2)^2]\}^{1/2}$, GooF $= \{\Sigma[w(F_o^2 - F_c^2)^2]/(n-p)\}^{1/2}$ where n = number of refl. and p = number of ref. parameters, $w = 1/[\sigma^2(F_o^2) + (0.1989 \cdot P)^2]$ where $P = (\mathrm{Max}(F_o^2, 0) + 2F_o^2)/3$.

and purity was established by C, H, N, S analysis, performed with an Elemental Vario EL2 instrument, and by ^{1}H NMR spectroscopy using a Bruker DRX 400 spectrometer with $B_1(^1\mathrm{H})$ = 400.0 MHz and TMS as standard.

Potentiometric titrations

All the reagents used were of analytical grade. All solutions were prepared with deionized water of MILLIPORE quality. The base used for potentiometric titration was carbonate-free 0.1 M NaOH, which was prepared from CO_2-free commercial concentrate (Merck Titrisol ampoules). A CO_2-free atmosphere for the base was ensured. Potentiometric measurements were performed with an apparatus consisting of a SCHOTT pH-meter CG825, fitted with glass and calomel reference electrodes (U402 M3/S7/60, Ingold), a 100 mL three-necked flask as the titration cell in a thermostat (25.00 ± 0.05 °C), and a 5 mL buret (BRAND, ±0.01 mL) which delivers the standard NaOH titration solution (MERCK Titrisol, 0.1 M) to the cell. A stream of oxygen-free N_2 gas was used in order to keep O_2 and CO_2 out of the titration cell and to stir the solution. The pH meter was calibrated with two buffer solutions (pH = 4.00 ± 0.02 and pH = 9.00 ± 0.02). The term p[H] in this paper is defined as $-\log [H^+]$, referring to the concentration of the hydrogen ion $[H^+]$ instead of its activity [7]. The direct pH meter readings were used in the calculations of the pK_a values. The value of $K_w = [H^+][OH^-]$ used in the computations was $10^{-13.78}$ mol^2·L^{-2}. The ionic strength was adjusted to 0.1 M by the addition of KCl as supporting electrolyte, and the total volume was 50.00 + 0.01 mL at the beginning of each potentiometric titration.

Refinement of the pK_a values

Protonation constants for **1** were calculated with the FORTRAN program BEST and were obtained through the algebraic solution of mass balance and charge balance equations evaluated at each equilibrium point of the formation curves [7]. The input for the program BEST consists of the components, concentrations of each component and initial estimates of the equilibrium constant for each species. The program refines stability constants by the iterative nonlinear least-squares fit of potentiometric equilibrium curves through a set of simultaneous mass balance equations for all the components expressed in terms of known and unknown equilibrium constants. The equilibrium constants reported in this paper were obtained as averaged values of three titrations. All the refinements converged at $\sigma < 0.025$ p[H] units of the observed p[H] value.

Crystal structure determination

Diffraction experiments were performed on a Nonius CAD4 diffractometer. The crystal structure was solved by Direct Methods and difference Fourier techniques (SIR-92) [8]. Structural refinement was done by full-matrix least-square routines on F^2 (SHELXL-97) [9]. Details of the crystal structure determination of HL and its crystal data are given in Table 2.

Theoretical methods

For *ab initio* calculations of **1** (HL) the GAUSSIAN 98 software package was used [10]. A Pople type 6-31G* basis set was generally employed. At the Hartree-Fock level of theory, initial geometry optimizations and calculations of vibrational frequencies were performed. Subsequent geometry optimizations and single point energy calculations, and analyses of the wavefunction in terms of natural bond orbitals (NBO) [11] were done using second order Møller-Plesset perturbation theory (MP2).

CCDC-685315 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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