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A THERMODYNAMIC STUDY OF THE PROTONATION OF SOME SULPHIDE-CONTAINING PYRIDINES AND AMINO-PYRIDINES IN AQUEOUS SOLUTION

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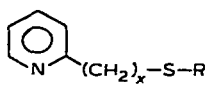
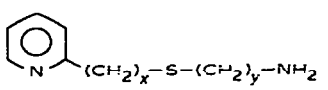
ABSTRACT

The protonation properties of pyridines with general formula



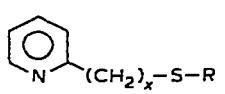
(R = CH_3, C_2H_5, CH_2CH_2OH; x = 1,2) and



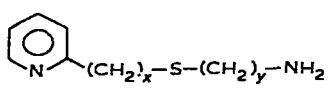
(x, y = 1,2; 1,3; 2,2; 2,3) have been investigated by potentiometry and calorimetry at 25°C in 0.5 mole dm^{-3} K{NO_3} solution. The protonation constants and the corresponding enthalpy and entropy changes are reported. The obtained values for the thermodynamic functions are discussed.

INTRODUCTION

As part of an investigation [1—4] on equilibria in aqueous solution of sulphide-containing amines and pyridines, we have now undertaken a thermodynamic study of a series of pyridines with general formula



(R = CH_3, C_2H_5, CH_2CH_2OH; x = 1,2) and



(x, y = 1,2; 1,3; 2,2; 2,3). The protonation constants of the ligands have been determined at 25°C in 0.5 mole dm^{-3} K{NO_3}. The corresponding

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enthalpies of reaction have been determined calorimetrically under the same conditions. From these values the corresponding entropy changes have been calculated.

It was the aim of this investigation to gain a better insight into the influence of an additional CH_2 group inserted between the electron-withdrawing sulphur atom and the nitrogen atom to be protonated.

EXPERIMENTAL

Abbreviations

The abbreviation for naming the ligands contains first the number(s) of carbon atoms between the donor groups, and then consecutively the donor group(s) present in the aliphatic chain. The IUPAC names, formulae and abbreviations are listed in Table 1.

Reagents

Pyridines of the type 2-N_pS(R) were prepared according to Kahmann et al. [5]. An appropriate amount of the corresponding mercaptan was added dropwise to 2-(chloromethyl)pyridine hydrochloride (Aldrich Chemicals) dissolved in an alcoholic solution of potassium hydroxide. After filtering the precipitated KCl and evaporating the alcohol on a rotavapor the remaining oil was distilled in vacuo. The residue was refractionated and only the middle fraction was taken.

Preparations of the pyridines 3-N_pS(R) were carried out by the same procedure but 2-mercaptoethylpyridine was added to the corresponding alkylbromide.

The molecular weights of these ligands were determined by means of a potentiometric titration of an acidified pyridine solution with standardized potassium hydroxide. Equivalence point calculations were performed using the method of Briggs and Stuehr [6].

The syntheses of 2,2-N_pSN and 2,3-N_pSN are also similar: to an alcoholic solution of HS—$(CH_2)_m$—NH_2 and NaOH, an equivalent amount of 2-picolylchloride hydrochloride was added. After refluxing for 2 h and filtering off precipitated NaCl, the final product was purified by fractional distillation in vacuo. The same procedure was followed for the synthesis of 3,2-N_pSN but this time 2-vinylpyridine (Fluka) was used as a starting product together with cysteamine. 3,3-N_pSN was obtained by adding 3-bromopropylamine hydrobromide (Aldrich Chemicals) to an alcoholic solution of KOH and 2-(2-mercaptoethyl)pyridine. More specifications about the synthesis of the bases n,m-N_pSN will be reported in a subsequent publication [7].

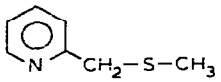
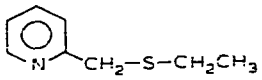
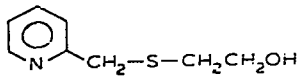
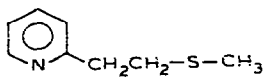
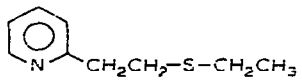
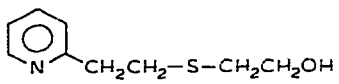
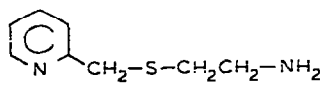
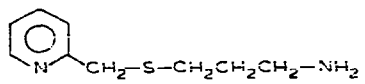
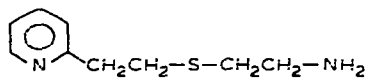
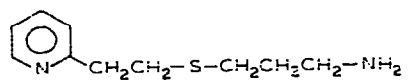
The molecular weights of the synthesized amino-pyridines were determined by titration with standardized HNO_3.

Solutions

Solutions of the different pyridines for the potentiometric and calorimetric study were prepared with CO_2-free twice distilled water and under a flow of

TABLE 1

The IUPAC names, formulae and abbreviations

IUPAC name	Formula	Abbreviation [a]
1-(2-Pyridyl)-2-thia-propane		2-$N_pS(CH_3)$ [b]
1-(2-Pyridyl)-2-thia-butane		2-$N_pS(C_2H_5)$
1-(2-Pyridyl)-4-hydroxy-2-thia-butane		2-$N_pS(C_2H_4OH)$
1-(2-Pyridyl)-3-thia-butane		3-$N_pS(CH_3)$
1-(2-Pyridyl)-3-thia-pentane		3-$N_pS(C_2H_5)$
1-(2-Pyridyl)-5-hydroxy-3-thia-pentane		3-$N_pS(C_2H_4OH)$
1-(2-Pyridyl)-4-amino-2-thia-butane		2,2-N_pSN [c]
1-(2-Pyridyl)-5-amino-2-thia-pentane		2,3-N_pSN
1-(2-Pyridyl)-5-amino-3-thia-pentane		3,2-N_pSN
1-(2-Pyridyl)-6-amino-3-thia-hexane		3,3-N_pSN

[a] N_p stands for the aromatic pyridine nitrogen.
[b] General abbreviation: n-$N_pS(R)$.
[c] General abbreviation: n,m-N_pSN.

nitrogen. Their concentrations were determined by potentiometric titrations with standardized nitric acid using Gran plots [8] and the calculation method of Briggs and Stuehr [6].

The potassium hydroxide solution was prepared from Titrisol ampoules (Merck) and the absence of CO_2 was checked weekly by Gran titrations. All solutions were made up to an ionic strength of 0.5 M K{NO_3}.

Potentiometric titrations

EMF readings were made on a radiometer digital potentiometer PHM 64 in combination with an Ingold HA 201 glass electrode, an Ingold 303-NS

calomel electrode (3 M KCl) and an Ingold 303-95 salt bridge containing 0.50 M KNO_3. Before and after each titration the electrode system was calibrated with an acid—base titration. The standard potential E_0 was determined from experimental EMF values using Gran's method [8]. The obtained value for the ionic product of water (pK_w = 13.72) is in good agreement with other literature values [9,10]. A purified nitrogen atmosphere was maintained in the titration vessel during titrations and all measurements were carried out at 25 ± 0.05°C. Experimental details for the potentiometric titration of the different pyridines are given in Table 2.

Calorimetric titrations

The calorimetric measurements were carried out with an LKB 8700/2 titration calorimeter, thermostatted at 25 ± 0.001°C. The titrant was added stepwise with an automatic piston burette (Tacussel Electroburap) equipped with a preselection unit. The solutions were kept at ionic strength I = 0.5 M by the addition of KNO_3. The heat Q generated at each titration step was determined according to the method described by Wadsö [11]. Experimental data are listed in Table 3.

TABLE 2

Experimental details for the potentiometric titrations

Pyridine	Pyridine (mmoles)	HNO_3 (mmoles)	Titre KOH	V_0 [a] (cm^3)
2-$N_pS(CH_3)$	1.2185	1.9079	1.0065	40.0
	1.1750	1.8991	0.9988	40.0
2-$N_pS(C_2H_5)$	1.5312	2.0344	1.0025	50.0
	1.0480	1.8133	1.0025	45.0
2-$N_pS(C_2H_4OH)$	1.4742	1.5140	1.0007	55.0
	1.1553	1.5140	1.0007	50.0
3-$N_pS(CH_3)$	1.4352	2.5160	1.0020	50.0
	1.1443	2.5160	1.0020	50.0
3-$N_pS(C_2H_5)$	1.5616	1.9940	1.0025	60.0
	0.7808	1.2610	1.0025	50.0
3-$N_pS(C_2H_4OH)$	1.4854	3.9736	1.0025	50.0
	1.0480	2.0346	1.0025	50.0
2,2-N_pSN	1.4794	3.5688	1.0050	51.0
	1.2500	3.1410	1.0015	50.0
2,3-N_pSN	1.2707	4.0640	1.0050	65.0
	1.1997	3.8873	1.0050	50.0
3,2-N_pSN	2.0500	4.5230	1.0010	80.0
	1.6194	4.0763	1.0030	60.0
3,3-N_pSN	1.5012	3.2788	1.0030	60.0
	1.0180	2.5365	1.0080	60.0

[a] Initial volume in the titration vessel.

TABLE 3

Experimental details for the calorimetric titrations

Pyridine	Pyridine (mmoles)	HNO_3 (mmoles)	Titre titrant HNO_3	Titre titrant KOH	V_0 [a] (cm^3)
2-$N_pS(CH_3)$	2.7984	2.9895		1.0037	75.0
2-$N_pS(C_2H_5)$	1.6290	2.9895		1.0037	75.0
2-$N_pS(C_2H_4OH)$	3.6855		0.5009		70.0
3-$N_pS(CH_3)$	2.8080	2.9895		1.0037	75.0
3-$N_pS(C_2H_5)$	1.7728	1.9930		1.0037	90.0
3-$N_pS(C_2H_4OH)$	3.7135		0.5009		70.0
2,2-N_pSN	6.0030	0.09790	0.4995		70.0
	6.0030		0.4995		70.0
2,3-N_pSN	3.9460	0.09790	0.4995		80.0
	5.8674		0.4995		92.0
3,2-N_pSN	6.0390	0.09790	0.4995		70.0
	6.0390		0.4995		70.0
3,3-N_pSN	3.6918	0.09790	0.4995		70.0
	5.2104		0.4995		80.0

[a] Initial volume in the titration vessel.

Calculations

The protonation constants for each of the pyridines were calculated by means of an appropriate FORTRAN IV program [3] based upon the variable metric method of Davidon [12]. The Q values corrected for dilution of the titrant and for the formation of water were used to calculate the enthalpy changes, ΔH with the aid of the program KALO [1]. All the programs were run on a SIEMENS 4004 computer. The values for the entropy changes, ΔS were derived from the obtained ΔH values and the protonation constants.

RESULTS AND DISCUSSION

The protonation constants and the corresponding thermodynamic functions are given in Table 4. Comparing 2-$N_pS(CH_3)$ with pyridine and 2-methylpyridine it is seen that the basicity of the first ligand is smaller and the enthalpy of protonation is less exothermic. However, the ligand 3-$N_pS(CH_3)$, characterized by an additional CH_2 group between the thioether and the pyridine group, has a basicity and protonation enthalpy almost identical to pyridine. Although it is known [14] that gas-phase basicities are attenuated in aqueous solution, as a result of compensating electrostatic solvation terms, it is still seen that the sulphur atom apparently reduces the electron density on the pyridine group, whereas insertion of a methylene group between S and pyridine reduces that electron-withdrawing effect.

As a general observation it can be seen that all investigated ligands may be divided into two series. The first series is characterized by one CH_2 group between the thioether group and the pyridine function and these ligands

TABLE 4

The protonation constants and corresponding thermodynamic functions [a,b]

Ligands	Pyridine group				Amino group			
	log K	$-\Delta G$	$-\Delta H$	$T\Delta S$	log K	$-\Delta G$	$-\Delta H$	$T\Delta S$
2-$N_pS(C_2H_5)$	4.720(4)	26.94(2)	19.3(1)	7.6(1)				
2-$N_pS(CH_3)$	4.723(4)	26.95(2)	19.7(2)	7.3(2)				
2-$N_pS(C_2H_4OH)$	4.613(5)	25.33(3)	20.5(2)	5.8(2)				
2,3-N_pSN	4.459(6)	25.45(3)	20.6(4)	4.8(4)	9.974(4)	56.92(2)	55.7(3)	1.2(3)
2,2-N_pSN	4.210(5)	24.02(3)	20.5(3)	3.5(3)	9.280(4)	52.96(2)	52.1(2)	0.9(2)
3-$N_pS(C_2H_5)$	5.330(3)	30.42(2)	22.4(2)	8.0(2)				
3-$N_pS(CH_3)$	5.331(3)	30.42(2)	22.7(2)	7.7(2)				
3-$N_pS(C_2H_4OH)$	5.277(3)	30.12(2)	23.5(3)	6.6(3)				
3,3-N_pSN	5.188(3)	29.61(2)	23.7(3)	5.9(3)	10.030(4)	57.24(2)	55.3(2)	1.9(2)
3,2-N_pSN	5.118(4)	29.21(2)	23.9(4)	5.3(4)	9.351(4)	53.37(2)	52.7(3)	0.7(3)
Pyridine [c]	5.31	30.4	22.6	7.8				
2-Methylpyridine [d]	6.02	34.3	27.4	6.9				

[a] 25°C; 0.5 mole dm^{-3} K$\{NO_3\}$; ΔG, ΔH and $T\Delta S$ in kJ $mole^{-1}$. Standard state: 1 mole dm^{-3}.

[b] Value in parentheses is the standard deviation on the last significant figure.

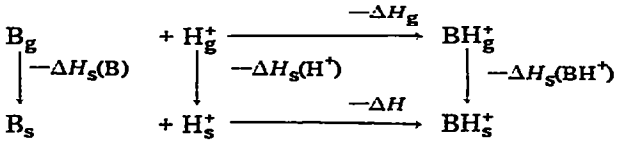
[c] Data from ref. 13: part IV — p. 165.

[d] Data from ref. 13: part IV — p. 167.

show a lower basicity ($-\Delta G$) than the corresponding ligand of the second series having one additional CH_2 group. In Table 5 we report the changes in the thermodynamic properties for the reaction

$$AH^+ + B \rightleftharpoons A + BH^+ \quad (1)$$

where A and B represent a ligand of each series. The data from Table 5 show that insertion of a CH_2 group causes an almost constant increase in exothermic heat of protonation $\delta(-\Delta H)$. The change in solution basicity, $\delta(-\Delta G)$, however, increases with the electron-withdrawing power of the substituent on the other side of the sulphur atom. It thus appears that a change in $-\Delta G$ is a better probe for the change of the internal or intrinsic basicity ($-\Delta G_g$) or proton affinity ($-\Delta H_g$) than $-\Delta H$. This may be explained by an alternation of the gas-phase basicities as a result of compensating electrostatic solvation terms.



Scheme 1. Thermodynamic cycle of protonation

From the thermodynamic cycle in Scheme 1 it can be concluded that the relative differences between the proton affinity in the gas-phase ($-\Delta H_g$) and in solution ($-\Delta H$) can only arise from differences in the heats of solvation of the neutral amines $\{\Delta H_s(B)\}$ and the charged ammonium ions $\{\Delta H_s(BH^+)\}$.

According to Aue et al. [14] the solvation of ions may be thought of as a two-step process: (1) the introduction of a neutral molecule of the same size as the ion into the solvent, and (2) the electrostatic interaction of the charge of the ion with the solvent. The following approximation may then be used

$$\Delta H_s(BH^+) \simeq \Delta H_s(B) + \Delta H_s(BH^+)^{el} \quad (2)$$

Taking into account this approximation it can be derived from the thermodynamic cycle that the relative differences in heat of protonation in solution

TABLE 5

Influence of an additional CH_2 group between S and the pyridine group on the protonation of the pyridine nitrogen [a]

	$\delta(-\Delta G)$	$\delta(-\Delta H)$	$\delta(T\Delta S)$
2-N_pS(C_2H_5) → 3-N_pS(C_2H_5)	+3.48	+3.1	+0.4
2-N_pS(CH_3) → 3-N_pS(CH_3)	+3.47	+3.0	+0.4
2-N_pS(C_2H_4OH) → 3-N_pS(C_2H_4OH)	+3.79	+3.0	+0.8
2,3-N_pSN → 3,3-N_pSN	+4.16	+3.1	+1.1
2,2-N_pSN → 3,2-N_pSN	+5.19	+3.4	+1.8

[a] All values in kJ $mole^{-1}$.

of reaction (1) reduce to

$$\delta\{-\Delta H\} = \delta\{-\Delta H_g\} + \delta\{-\Delta H_s(BH^+)^{el}\} \quad (3)$$

When inductive effects operate to increase the proton affinity ($-\Delta H_g$) of the pyridine nitrogen, the pyridinium ion usually has a lower charge density at nitrogen and should be less solvated than normal, thus leading to a decrease in $-\Delta H_s(BH^+)^{el}$ and an attenuation of the heat of protonation in solution ($-\Delta H$). The higher the change in inductive effect by insertion of an additional CH_2 group between the thioether and the pyridine group, the higher the decrease in charge density and solvation of the pyridinium ion. This might be the reason for the almost constant increase $\delta(-\Delta H)$ found in Table 5.

Relative differences in the entropy term or $\delta(T\Delta S)$ must result almost entirely from the solvation terms $T\Delta S_s(B)$ and $T\Delta S_s(BH^+)$, since the gas-phase entropy change may be thought to be the same for all pyridines.

As for the enthalpy term, the entropy term $T\Delta S_s(BH^+)$ can be divided into a hydrophobic term equal to $T\Delta S_s(B)$ and a remaining electrostatic term $T\Delta S_s(BH^+)^{el}$. The relative changes of the protonation entropy in solution [see eqn. (1)] may thus be attributed mainly to relative changes in the electrostatic solvation entropy term

$$\delta\{T\,\Delta S\} \simeq \delta\{T\,\Delta S_s(BH^+)^{el}\} \quad (4)$$

The higher the decrease in electron-withdrawing power on insertion of a CH_2 group between S and the pyridine group, the higher the decrease in charge density, the less solvated will be the pyridinium ion and the higher the relative increase in protonation entropy in solution (see Table 5).

The influence on the thermodynamic properties of protonation by addition of a CH_2 group to the other side of the pyridine group is given in Table 6. As is expected, the influence on the basicity of the pyridine group is almost negligible. Only in those cases where the electron-withdrawing effect of a further substituent (ammonium group) is attenuated, the basicity in solution increases slightly. Here too and for the same reasons the relative increase in intrinsic basicity $\delta(-\Delta G_g)$ or proton affinity $\delta(-\Delta H_g)$ is best reflected by the relative increase in solution basicity $\delta(-\Delta G)$.

TABLE 6

Influence of an additional CH_2 group to the other side of S on the protonation of the pyridine nitrogen [a]

	$\delta(-\Delta G)$	$\delta(-\Delta H)$	$\delta(T\Delta S)$
3-N_pS(CH_3) → 3-N_pS(C_2H_5)	0.00	−0.3	+0.3
2-N_pS(CH_3) → 2-N_pS(C_2H_5)	−0.01	−0.4	+0.3
3,2-N_pSN → 3,3-N_pSN	+0.40	−0.2	+0.6
2,2-N_pSN → 2,3-N_pSN	+1.43	+0.1	+1.3

[a] All values in kJ $mole^{-1}$.

TABLE 7

Influence of an additional CH_2 group on the protonation of the amino nitrogen [a]

	$\delta(-\Delta G)$	$\delta(-\Delta H)$	$\delta(T\Delta S)$
2,2-N_pSN → 2,3-N_pSN	+3.96	+3.6	+0.3
3,2-N_pSN → 3,3-N_pSN	+3.87	+2.6	+1.2
2-NS(CH_3) → 3-NS(CH_3) [b]	+3.55	+2.0	+1.6
2,2-N_pSN → 3,2-N_pSN	+0.41	+0.6	−0.2
2,3-N_pSN → 3,3-N_pSN	+0.32	−0.4	+0.7
2-NS(CH_3) → 2-NS(C_2H_5) [b]	−0.16	−0.1	−0.1

[a] All values in kJ $mole^{-1}$.
[b] Data from ref. 1.

As can be deduced from Table 4 the protonation entropy of the amino nitrogen is less favourable than the protonation entropy of the pyridine nitrogen. This may be ascribed to the greater polarizability of the ammonium ion. The influence of an additional CH_2 group on the protonation of the amino group is given in Table 7. Insertion of a methylene group between the amino nitrogen and the electron-withdrawing sulphur atom increases the basicity $-\Delta G$. In this case too, the observed increase is largely due to an increase in protonation enthalpy $-\Delta H$.

As contrasted with the behaviour of the pyridine group, the relative differences of the protonation heat $\delta(-\Delta H)$ are not constant, but do increase with increasing negative inductive effect of the second substituent of the thioether group. Also in contrast with the behaviour of the pyridine protonation is the trend in relative differences of the entropy term: although a higher increase in protonation entropy is expected if a further electron-withdrawing substituent is present, the reverse trend is found. The same trend, opposite to that expected for an electrostatic effect, is also found in either a series of primary or secondary or tertiary amines [14]. According to Aue et al. [14] this could be the result of the fact that the hydrophobic effects have not been fully subtracted out of the electrostatic term $T\Delta S(BH^+)^{el}$ [see eqn. (2)].

The influence of an additional CH_2 group on the other side of the sulphur atom (Table 7) on the protonation of the amino nitrogen is almost negligible, as is expected.

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