Formation of Hydrogen-bonded Complexes between Phenol and Some Heterocyclic Bases in Carbon Tetrachloride

Miklós Orbán, Ágnes Kiss, and Lajos Barcza *
Institute of Inorganic and Analytical Chemistry, L. Eötvös University, H-1088 Budapest, Múzeum krt. 4B, Hungary

The mixtures of phenol and some heterocyclic bases of biological importance have been studied by i.r. spectroscopy in CCl_4 and equilibrium constants (K) and thermodynamic data (ΔH, ΔG, ΔS) have been determined at 25 and 40 °C. The formation constants of hydrogen-bridged phenol complexes were found to be related to the protonation constants of the bases, but no strict linearity can be proved in many cases. The participation of the non-bonded electron pair of the heteroatom in the π-system of the rings plays a dominating role in the proton-acceptor processes.

Many heterocyclic bases (pyrrole, pyrimidine, pyrazine, *etc.*) and especially their derivatives are of biological importance. The biological activities of these compounds are mostly influenced by their proton-acceptor abilities.

To characterize and to compare the hydrogen-bonding (proton-acceptor) ability of the bases, complex formation with phenol (or substituted phenols) has been studied for many years.[1] The methods used are based mainly on i.r. and n.m.r. spectroscopy and the spectra are usually taken in inert or nearly inert solvents, mostly in carbon tetrachloride.

The correlation between the protonation constant (measured in aqueous solution) of a base and the formation constant (or enthalpy change) of its hydrogen-bonded complexes has been established and discussed.[2–8] The general conclusion was drawn that a linear dependence exists only for related proton acceptors. The relationship is, however, not always straight-forward and must be proved experimentally.

Only a few references can be found in the literature about the thermodyamic data of hydrogen-bridged complexes of the heterocyclic bases. It may be of interest to study the relationship between the enthalpy and entropy changes as well, since a close relationship between these thermodynamic data, supported by theoretical considerations, has already been demonstrated for some hydrogen-bridged systems.[1,9] The aim of this paper is to clarify some aspects in the interaction of some heterocyclic bases with phenol in CCl_4 solution.

Experimental

The solvent was of analytical grade purity and was further purified as follows. Concentrated sulphuric acid (10% of the total volume) was added and the mixture was shaken thoroughly. After separation of the layers the organic phase was extracted first by water, then neutralized by sodium carbonate solution, and washed again with water. The wet carbon tetrachloride was dried over $Mg(ClO_4)_2$ and distilled from granulated potassium hydroxide before use.

The compounds studied are listed in Table 1. Phenol itself, as well as pyridazine, pyrrole, pyrrolidine, piperidine, and pyridine were distilled before use. The purification of the thiophene was done as follows: first it was dried over $Mg(ClO_4)_2$, then distilled from solid KOH–$KMnO_4$ mixture. The other compounds were of high purity and could be used directly.

Since phenol is known to exist partly in dimerized[10] or even in trimerized[11] form in CCl_4 solution, for the sake of simplifying the calculations the concentration of phenol did not exceed 10^{-2} mol dm^{-3}.

The concentrations of the proton acceptor bases were usually equal to or greater (at most 20 times) than that of phenol. Use of

Table 1. Formation constants of hydrogen-bridged phenol complexes in CCl_4

Base		K_{25} °C	K_{40} °C
Pyridazine *		47.2 ± 1.4	27.0 ± 0.8
Pyrimidine *		18.1 ± 0.6	10.9 ± 0.4
Pyrazine *		14.7 ± 0.6	9.3 ± 0.2
Piperazine	K_1	205.0 ± 2.4	103.0 ± 5.6
	K_2	27.0 ± 2.0	22.0 ± 1.0
2,5-Dimethylpiperazine	K_1	143.0 ± 1.0	80.0 ± 1.6
	K_2	20.3 ± 0.7	14.9 ± 1.1
Piperidine		151.0 ± 2.0	79.0 ± 2.0
Pyridine		51.9 ± 1.0	31.9 ± 0.5
Pyrrolidine		225.0 ± 1.0	115.0 ± 1.2
Pyrrole		2.6 ± 0.6	1.9 ± 0.5
Thiophene *		0.40 ± 0.03	0.31 ± 0.01
Furan *		0.17 ± 0.01	0.11 ± 0.01

* Constants were determined both from the decrease of the free OH intensities and from the blue-shifted OH $\cdots$ N band.

these high ratios allowed us to control the homoconjugation of phenol, *e.g.* at both 20:1 and 1:5 base–phenol ratios the same equilibrium constants could be calculated, providing that the monomeric form of the free phenol is present under our experimental conditions. For detecting any 2:1 phenol–base complexes, an excess of phenol must be used. With the exception of piperazine and its 2,5-dimethyl derivative no other examples of 2:1 phenol–base stoicheiometry were found. Even in the pyridazine, pyrimidine, and pyrazine systems only 1:1 hydrogen-bonded complexes were present.

Some disturbing effect (colour and/or precipitate formation) was observed on using pyrrolidine and piperazine (regarded as the strongest bases) when used in high concentration. This phenomenon[12] can be eliminated by using freshly prepared solutions with CCl_4 purified with extreme care.

I.r. spectra have been recorded with a Unicam SP 700 spectrophotometer at 25.0 ± 0.1 and 40.0 ± 0.1 °C. The most marked and rather sharp band is at 3 611 cm^{-1} characteristic of the free (monomeric) phenolic hydroxy group. (The intensity of the peak at and under 10^{-2} mol dm^{-3} is strictly linear with the concentration of free phenol.)

The absorption of the OH $\cdots$ N bond can be well observed at lower frequencies and its intensity is linear with the concentration of the hydrogen-bonded complex. (The shift in the OH frequencies due to hydrogen-bond formation is known to be linearly related to enthalpy changes in the process.[13,14]) Unfortunately, as the shifts increase the band widths are increased, causing uncertainties in the determination of the peak intensities.

Both the free OH peak and the complexed OH $\cdots$ N band have been used for the determination of K values in five systems (see Table 1). In other systems the band intensity at 3 611 cm^{-1} has been used since this peak allows us to calculate the concentration of monomeric phenol with good precision.

From the total and free phenol concentrations the complex (and the free base) concentrations can be calculated (assuming only 1:1 association): $[D]_T = [D] + [D \cdot A]$ and $[A]_T = [A] + [D \cdot A]$ where D stands for the proton donor phenol and A for the proton acceptor base.

The equilibrium constant is given by equation (1). The errors

$$K_1 = \frac{[D \cdot A]}{[D][A]} = \frac{[D]_T - [D]}{[D]([A]_T - [D]_T + [D])} \quad (1)$$

in the measurements accumulated in the values of free base concentration. To decrease the standard deviation, all systems were measured for at least eight phenol–base ratios and parallel measurements were carried out. The equilibrium constants differed within an acceptable range and in 9 systems out of 11 no trend in the K values was observed as the proton donor–acceptor ratio was varied.

Piperazine and 2,5-dimethylpiperazine form 2:1 phenol–base complexes. The formation constants of the 1:1 complex have been measured at relatively low ratios of phenol to base. The formation constant of the ternary complex is defined by equation (2) and can easily be computed, using known and measured values.

$$K_2 = [A \cdot D_2]/[A \cdot D][D] \quad (2)$$

Formation constants together with standard deviations are summarized in Table 1.

Stability constants measured at two different temperatures made it possible to obtain enthalpy (ΔH) and entropy (ΔS) values for hydrogen-bond formation. The values are listed in Table 2 which also contains ΔG values (at 25 °C) as well as pK_A values of bases at the same temperature in aqueous solution.[15] (The standard deviations of thermodynamical parameters are not given as they can be derived from the data given in Table 1.)

Discussion

According to literature data [16] a correlation is expected between the protonation constants of the bases and the thermodynamic parameters of their hydrogen-bridged complexes with phenol in CCl$_4$. But the relationship is linear only in case of the three diazines (pyrazine, pyrimidine, and pyridazine): $pK_A - \Delta H$, $pK_A - \Delta G$ or $pK_A - \lg K_1$ plots can be demonstrated to give a straight line. Even the ΔH–Δv (shift of OH frequency due to the formation of hydrogen-bonded complexes) plot is linear. Shift is ca. 350—400 cm^{-1}, which suggests n-type proton acceptability. (Benzene is unambiguously a π-type proton acceptor as the Δv value for its phenol complex is only 48 cm^{-1}.[17])

The rather low stability constants of the three unsaturated diazine complexes and the fact that association occurs only with one phenol molecule can be attributed to their aromatic character. The Δv values, however, indicate that the nitrogen participates in the hydrogen bond as an n acceptor. The existence of 2:1 phenol–diazine associates is not excluded even in the concentration range used; however, the K_2 formation constants are at least two orders of magnitude lower than those of 1:1 complexes. (This is not very surprising since their second protonation constants are also very small, see Table 2.)

The basicity and hydrogen-bonding ability of the heterocyclic compounds are influenced first of all by their aromatic or aliphatic character. The difference in the stability constants of 1:1 phenol complexes of pyrrolidine and pyrrole is about two orders of magnitude, that of piperazine and pyrazine is greater than an order of magnitude, and it is significant for piperidine and pyridine.

Both piperazine and its 2,5-dimethyl derivative are dibasic in aqueous solution and form stable 1:1 and 2:1 phenol complexes in CCl$_4$ solution. It is surprising that both 1:1 and 2:1 phenol–piperazine complexes are more stable than those of 2,5-dimethyl-piperazine, since an alkyl substituent usually increases the pK value of a base. The explanation of the lower stability is a steric effect, i.e. the hydrogen bonds (even protonation) are probably hindered by methyl substitutions of carbon next to nitrogen.

For the four five-membered heterocyclic compounds, the extreme stability of the pyrrolidine–phenol complex is expected. In this case bonding occurs between the non-bonding electron pair of nitrogen and the hydrogen atom of the phenolic hydroxy. The remarkably low stability of pyrrole, furan, and thiophene associates with phenol is due to the weak interaction between the π-system of the ring and the phenolic proton. This view is supported by the low Δv values (ca. 50 cm^{-1}) found in these systems.

Summarising the results the following conclusions can be drawn: (i) a weaker base usually forms a less stable hydrogen-bridged complex than a stronger base; (ii) the Δv value for a more stable complex is always greater than that for a less stable one; (iii) the assumed parallel change in ΔH and ΔS values is valid unless extremely low stability constants with relatively high errors are used to derive these data; (iv) the stability of the three phenol–aromatic diazine complexes is influenced by the relative position of the two nitrogen atoms in the ring, the most symmetrical pyrazine forming the least stable associate and the least symmetrical pyrazine the most stable one and distortion of the π-system favouring the formation of more stable hydrogen-bridged complexes; (v) the participation of electrons of the heteroatom in the π-system plays the most important role in the proton-acceptor ability of the heterocyclic compounds.

Table 2. Thermodynamical parameters* of phenol associates and pK values of the bases

Base	$-\Delta H^\circ/$ kJ mol^{-1}	$-\Delta S^\circ/$ J mol^{-1} K^{-1}	$-\Delta G^\circ/$ kJ mol^{-1}	$\lg K_A$ [15]
Pyridazine	28.9	64.5	9.6	2.24
Pyrimidine	26.4	64.5	7.1	1.23
				−6.3
Pyrazine	23.9	57.4	6.7	0.65
				−5.8
Piperazine	35.6	75.8	13.0	9.81
	10.5	8.4	8.0	5.55
2,5-Dimethyl piperazine	30.1	59.4	12.1	9.66
	15.9	28.5	7.5	5.20
Piperidine	33.5	70.3	12.6	11.11
Pyridine	25.1	51.1	9.6	5.25
Pyrrolidine	34.8	71.6	13.4	11.27
Pyrrole	16	46	2.3	−3.8
Thiophene	13	50	−2.3	
Furane	20	100	−4.4	

* The ΔH values were calculated from the relationship: $\lg K_2/K_1 = \Delta H \cdot (T_2 - T_1)/4.567 T_2 T_1$ where ΔH is the heat of interaction and which does not change in the $T_2 - T_1$ interval. The ΔG and ΔS values are for 25 °C.

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