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Hydrogen Bonding Properties of Pharmaceuticals. Part 1. 2,3,4,5-Tetraiodo, Tetrabromo and Tetrachloropyrroles as Medium-Strong Proton Donors

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Heteroassociation of 2,3,4,5-tetraiodopyrrole and its bromo and chloro analogues with acetone, tetrahydrofuran, pyridine, dimethyl sulphoxide, and hexamethylphosphorictriamide in carbon tetrachloride was studied by means of infrared spectroscopy. Values of the formation constants for 1 : 1 complexes and the $\Delta\nu$NH frequency shifts of these acid-base pairs are reported. The proton donor strengths of the halogenated pyrroles were found to be of the same order of magnitude as that of phenol. In most cases the structure of the bonded NH stretching absorption is irregular, containing several maxima and minima. The reasons for this irregularity are discussed.

INTRODUCTION

Iodine has long had a strong position as a general disinfectant and continues to maintain that position in a variety of new product forms[1]. One of the most successful developments in recent years has been the appearance of iodophors, i. e. organoelemental iodine complexes which gradually release the available iodine. There are also some organic iodine compounds whose effect is, to some extent, similar to that of iodine. Tetraiodopyrrole C_4I_4NH is used externally, in a variety of ointments and suspensions, as a topical anticeptic[1,2].

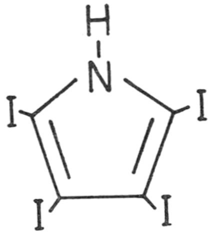

Figure 1. The structure of tetraiodopyrrole.

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The importance of hydrogen bonding in biological systems is generally recognized. From a purely chemical point of view the tetrahalogenated pyrroles are of some interest because pyrrole itself has been widely used as a standard acid in hydrogen bond studies. Four highly electronegative halogen substituents are assumed to make the NH bond more acidic. Here we report the results obtained for the proton donor properties of tetrahalogenopyrroles.

EXPERIMENTAL

Chemicals. Acetone (E. Merck A. G., Darmstadt, p. a. grade), tetrahydrofuran (THF, p. a. from E. Merck A. G.), dimethyl sulphoxide (DMSO, zur Synthese, E. Merck A. G.), pyridine (Py, Baker Analyzed Reagent, Noyry-Baker N. V., Deventer, Holland), hexamethylphosphorictriamide (HMPA, UVASOL from E. Merck A. G.), and carbon tetrachloride (UVASOL from E. Merck A. G.) were purified by usual methods as described previously[3,4]. Perdeuterated bases (acetone-d_6, tetrahydrofuran-d_8, pyridine-d_5, DMSO-d_6, and HMPA-d_{18}) were UVASOL grade from E. Merck A. G. and were used as received.

Tetraiodopyrrole (TIP) was obtained from two different sources. The commercial product (Chemical Producements Laboratories, Inc., College Point, N. Y.) was crystallized several times from ethanol-water. Several batches were synthesized with a slightly modified method from the literature[5,6]. All the different batches gave identical results. Tetrabromopyrrole (TBP) was synthesized from freshly distilled pyrrole (dissolved in 96% ethanol), treated with bromine. The crude product was crystallized several times from ethanol. In synthesizing tetrachloropyrrole (TCP), pyrrole was dissolved in ether to which sulphuryl chloride was added. The product was first steam distilled and then sublimed or crystallized from petroleum ether.

The stability of tetrahalogenopyrroles varies considerably. Tetraiodopyrrole can be stored in the dark for several months with only slight darkening, presumably due to liberation of iodine. Tetrabromopyrrole can be stored for about one week before considerable decomposition occurs. Tetrachloropyrrole was found to be relatively unstable and could be stored in the dark (in a dessicator) for only about two days before appreciable decomposition begins, leading to fast complete destruction of the product presumably with an autocatalytic mechanism. By storing it under petroleum ether, however, it can be stored for several days.

Spectrometric measurements. Near-infrared spectra for the determination of formation constants K_{11}, and $\Delta\nu$NH values, were obtained with a Beckman DK-2A spectrophotometer equipped with a thermostated cell holder. The procedures used in recording of the spectra and the preparation of solutions have been reported previously[3,4]. Concentrations were corrected for the thermal expansion of the solvent.

The IR spectra of various halogenopyrrole — base complexes were recorded with a Perkin-Elmer 577 spectrometer at ambient temperature using 5 mm cells with KBr windows. In most cases perdeuterated bases were used to avoid the disturbing influence of the CH stretching vibrations of the bases on the hydrogen bonded NH stretching absorption. The solid state spectra for pure TIP, TBP and TCP were obtained by the usual KBr tablet technique.

To our knowledge no spectral data for tetrahalogenated pyrroles have been reported previously. We found the following IR absorptions in the solid state (KBr disk, in cm^{-1}).

TIP: 3357 (s), 1469 (m), 1384 (m), 1278 (m), 1225 (m), 1036 (w), 943 (m), 600 (m), 504 (s), 482 (m), 230 (w, CsI disk).

TBP: 3395 (s), 1518 (s), 1398 (m), 1328 (m), 1251 (m), 990 (w), 965 (s), 600 (m), 495 (s), 460 (w).

TCP: 3400 (s), 1550 (m), 1482 (w), 1411 (m), 1360 (m), 1352 (sh), 1272 (m), 1260 (w), 1007 (m), 932 (w), 695 (m), 607 (m), 572 (w), 526 (w), 463 (s).

There may be slight discrepancies in values due to the Christiansen effect[7] which could not be completely avoided.

Calculations. The values of the formation constants K_{11} of the 1 : 1 hydrogen bonded complexes were calculated from equation (1):

$$K_{11} = \frac{1 - A/A^0}{A/A^0\,[c_B{}^0 - c_A{}^0\,(1 - A/A^0)]} \tag{1}$$

where c_A^0 is the total (initial) molar concentration of the pyrrole, c_B^0 that of the base, and A^0 and A are the absorbances at the frequency of the stretching vibration of the free NH group before and after complex formation, respectively.

RESULTS AND DISCUSSION

Values of K_{11} and $\Delta\nu$NH

A summary of the values obtained for the complexes of TIP, TBP and TCP with various bases is presented in Table I. For comparison, the values for analogous pyrrole complexes were also measured under the same conditions: Comparison of the K_{11} values shows that tetrahalogenated pyrroles are remarkably better hydrogen bond donors than pyrrole[8] itself. In Figure 2

TABLE I

Values of the K_{11} and $\Delta\nu$NH for the 1 : 1 Complexes of Tetrahalogenated Pyrroles with Bases at 25 °C

Base	TIP		TBP		TCP	
	K_{11} l mol^{-1}	$\Delta\nu$NH cm^{-1}	K_{11} l mol^{-1}	$\Delta\nu$NH cm^{-1}	K_{11} l mol^{-1}	$\Delta\nu$NH cm^{-1}
Acetone	12.0	203	22.4	232	31.2	265
THF	17.8	312	33.7	325	51.8	318
Pyridine	77.6	>355	140	>352	—	—
DMSO	201	>367	606	>359	791	>338
HMPA	952	>408	17900	>383	15400	>346

Solvent: carbon tetrachloride.

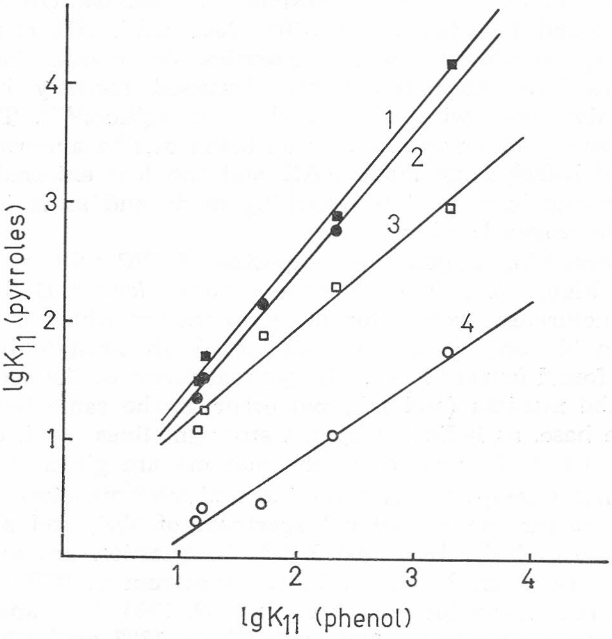

Figure 2. The plots of lg K_{11} (pyrroles) against lg K_{11} (phenol). Curve 1: tetrachloropyrrole, Curve 2: tetrabromopyrrole, Curve 3: tetraiodopyrrole, Curve 4: pyrrole.

the values of the logarithms of the formation constants are plotted against the corresponding values for phenol obtained from literature[4,9]. The plots reveal that the hydrogen bonding ability of halogenated pyrroles is of the same order of magnitude as that of phenol. The reported[4] value for a phenol — THF complex, for instance, is K_{11} about 16 l/mol (at 25 °C) and that for phenol — DMSO 185 l/mol, the corresponding values for TIP — THF being $K_{11} = 17.8$ l/mol and for TIP — DMSO $K_{11} = 201$ l/mol.

Comparison of the frequnecy shift values is possible only when acetone or THF are used as bases, because the band profiles are irregular in form with stronger bases (see below). For the THF-pyrrole complex the value of $\Delta \nu$ NH is 143 cm^{-1} and for the THF-phenol complex[9] the value of $\Delta \nu$ OH is 284 cm^{-}1, as compared to the values of $\Delta \nu$ NH of 312 cm^{-1}, 325 cm^{-1}, and 318 cm^{-1} obtained for the THF complexes of TIP, TBP, and TCR, respectively. Also these values indicate the similarity in the hydrogen bonding tendency of tetrahalogenated pyrroles and phenol, regardless of the fact that some precaution may be needed when comparing $\Delta \nu$ OH values with $\Delta \nu$ NH values.

Structure of the bonded NH absorption

Hydrogen bonds can be classified as weak, intermediate and strong with $\Delta \nu / \nu_0$ values of about $<12\%$, 12—22% and 25—85%, respectively[10]. In the case of weak hydrogen bonds the bonded stretching band is usually reasonably regular in form and the frequency shifts $\Delta \nu$ AH are easy to measure. Strong hydrogen bonds, on the other hand, mostly show the A, B, C patterns which mav be attributed to Fermi resonance of ν AH with 2 δ AH and 2 γ AH[11].

'or medium strong hydrogen bonds the band profile can be still more complicated, containing several submaxima. The bonded OH stretching absorptions are found between about 3100—2800 cm^{-1}, NH stretching bands occurring perhaps at sligthly lower frequencies. The reasons for the complex band structures have been thoroughly discussed recently by Hadži and Bratos[11], and also dealt with by several other authors[12-15]. The absorption patterns are usually interpreted either as being due to anharmonic coupling between the high-frequency mode ν AH and the low external mode ν_σ, or to Fermi resonance between the stretching mode and some internal modes perturbed by hydrogen bonding.

The NH stretching region for complexes of TIP with various bases is reproduced in Figure 3. For the acetone complex (curve 1) the bonded absorption is structureless, except for the unsymmetry which is usually found when hydrogen bonding occurs to a ketone[4]. With stronger bases multiplet structures are found (curves 3—5). The general forms of the spectra are quite similiar, i. e. the maxima (and minima) occur at the same frequencies irrespective of the base, as indicated by the strainght lines (a—f) connecting the maxima in Figure 3. The values of the maxima are given in Table II.

We shall not attempt to interpret the multiplet structure until a reasonable assignment for the vibrational spectrum of TIP, and some estimates of the frequencies of the hydrogen bonds in question are available. Some comments may, however, be made. In the spectrum of TIP there are four absorptions in the region 1500—1200 cm^{-1}: 1469, 1384, 1278 and 1225 cm^{-1} in KBr, the solution values being 1466 cm^{-1} (CCl_4), 1387 cm^{-1} (CCl_4), 1274 cm^{-1} (CS_2) and 1219 cm^{-1} (CS_2). The combinations and overtones of H-sensitive 1466,

TABLE II

Frequency Values of the Submaxima of the NH *Stretching Bands of the Tetraiodopyrrole — Base Complexes at Ambient Temperature*

Base	a	b	c	d	e	f
Acetone-d_6	3240	2975	2880	—	—	—
THF-d_8	3130	2975	2880	2810	(2700)	(2600)
DMSO-d_6	3080	2967	2867	2803	2695	2600
Py-d_5	3065	2953	2848	2790	2696	2610
HMPA-d_{18}	3028	2940	2835	2777	2685	2603

For letters a—f refer to Figure 3.

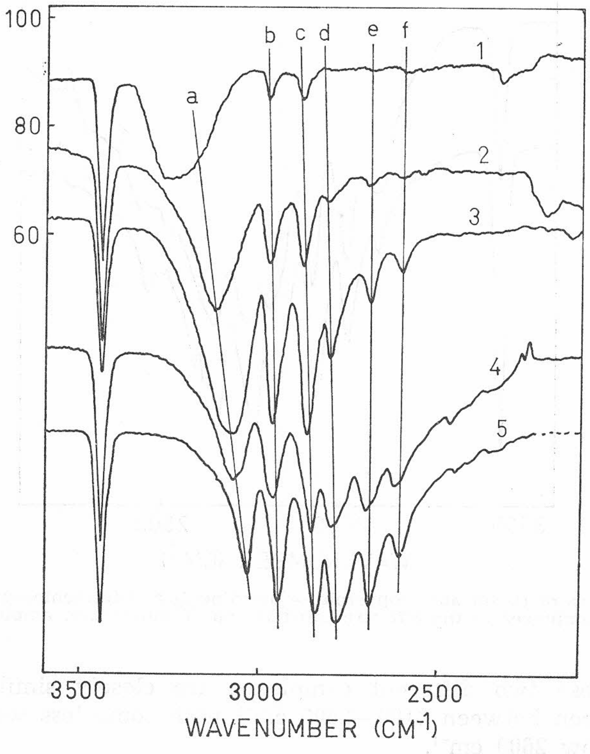

Figure 3. IR spectra of tetraiodopyrrole — base complexes in the NH stretching region. Bases: 1. acetone-d_6, 2. THF-d_8, 3. DMSO-d_6, 4. pyridine-d_5, 5. HMPA-d_{18}. Symbols a—f are explained in the text. Temperature: ambient.

1387 and 1219 cm^{-1} bands lead to the values 2932, 2853, 2774, 2675 and 2606 cm^{-1} which are quite close to the values of the 2nd, 3rd, 4th, 5th and 6th maxima in Table III.

The spectra of the weaker hydrogen bonded complexes reveal some interesting features. The submaxima at about 2975 cm^{-1} and 2880 cm^{-1} fall clearly outside the region of the ν NH band of the TIP-acetone complex (Figure 3, curve 1), and seem to have gained some intensity due to Fermi resonance. The interpretation of the spectrum of TIP-THF complex (curve 2 in Figure 3) is somewhat more difficult. Our opinion is that the first maximum at 3130 cm^{-1} is the »true« maximum for the 1 : 1 complex so that it can be used in estimating the $\Delta \nu$ NH value. If so, the following maxima fall at the end of the NH stretching region. It can be seen that the maxima on the b and c lines are quite pronounced but also the maxima on lines d, e and f are clearly seen.

Also the structures of NH stretching absorptions for complexes formed by TBP and TCP show similar patterns as those for TIP. The spectra of TBP-pyridine and TCP-HMPA complexes are reproduced in Figure 4. The spectra of these two different complexes are closely similar: six distinct maxima are seen between 3100—2600 cm^{-1} with some less well-defined structure also below 2600 cm^{-1}.

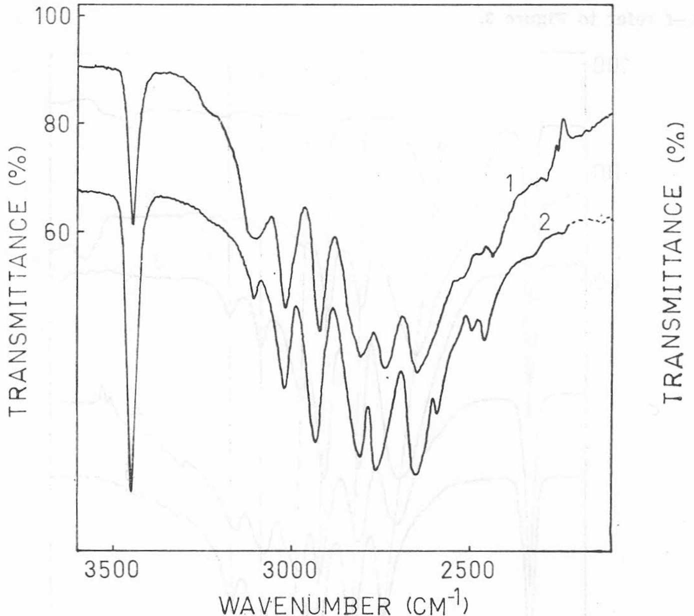

Figure 4. IR spectra of (1) tetrabromopyrrole — pyridine-d_5 and tetrachloropyrrole — HMPA-d_{18} complexes in the NH stretching region. Temperature: ambient.

CONCLUSIONS

The following conclusions can be drawn from the results of this study. Tetrahalogenated pyrroles are medium-strong proton donors. The complexes formed by these acids with bases would be suitable model systems in studying the origin of the submaxima of the ν AH stretching bands. If perdeuterated bases are used there is no disturbing absorption due to CH groups in the NH stretching region. In addition, the geometry of the complexes is well defined, this being especially true for tetrahalogenopyrrole — pyridine complexes which are linear and probably also planar.

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IZVLEČEK

Vodikove vezi v farmacevtskih substancah. Prvi del. 2,3,4,5-tetrajodo-, tetrabromo- in tetrakloropirol kot srednje močni protonski donorji

Antti Kivinen, Helena Auvinen, Jarmo Huuskonen in Keijo Väkiparta

Članek je posvečen študiju heteroasociacije 2,3,4,5-tetrajodopirola (TIP) in njegovih bromo- in kloro-analogov z acetonom, tetrahidrofuranom (THF), piridinom, dimetilsulfoksidom in heksametilfosfortriamidom (HMPA) v ogljikovem tetrakloridu. Vrednosti asociacijskih konstant K_{11} (kompleks 1 : 1) so dobljene z merjenjem intenzivnosti infrardečih trakov, ki ustrezajo valenčnemu nihanju NH-skupin, in so podane skupaj z vrednostmi $\Delta\nu$, premika frekvence νNH, v tabeli 1. Tipične vrednosti $\Delta\nu$ se spreminjajo od 203 cm^{-1} za kompleks TIP-aceton ($K_{11} = 12{,}0$ l/mol) do vsaj 408 cm^{-1} za kompleks TIP-HMPA ($K_{11} = 952$ l/mol). Primerjava s podobnimi kompleksi pirola in fenola pokaže, da so halogenirani piroli znatno močnejši protonski donorji kot sam pirol in se obnašajo podobno kot fenoli. Posebnost absorpcijskih trakov νNH teh kompleksov je njihova zapletena struktura, ki kaže številne submaksime. Frekvence teh submaksimov ne zavisijo od baze.