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Spectroscopic Analysis of Charge Transfer Complexes between Morpholine and Iodine

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It has been demonstrated spectroscopically that many nitrogen-containing heterocyclic compounds can form charge transfer complexes with iodine. The complexes of morpholine with iodine were shown to be of the n-σ type with a 1 : 1 stoichiometry. A strong donor–acceptor interaction was found ($K_c = 1261 \pm 12\,\mathrm{mol}^{-1}$ at 20 °C in CCl_4), considerably higher than those of complexes of aromatic compounds with iodine. The high value of the formation constant for this complex indicated that morpholine could serve as a starting point for the synthesis of novel anti-thyroid drugs.

Keywords morpholine; iodine; charge-transfer complex; anti-thyroid drug

Spectroscopic analysis has demonstrated that many nitrogen-containing heterocyclic compounds form charge transfer complexes with iodine.[1-4] The value of formation constant K_c of the complex with iodine has been used as a criterion for evaluation of potential anti-thyroid activity of such compounds.[3,5,6]

The morpholine structure is found in many compounds of pharmacological importance, including antiviral agents (moroxydine, morazine), analgesics (morpheridine), antitussives (pholcodine), muscle relaxants (flumetramide), anxiolytics (molindine) and antiparasitics (minorazole). In order to assess potential activity of such compounds towards the thyroid gland, the chemical reactivity of morpholine with molecular iodine was investigated, and the formation constant of its charge transfer complex with iodine was determined.

Experimental

Iodine was bisublimed (Merck Suprapur 4763). It was kept in the dark in a dessicator containing P_2O_5. Morpholine or tetrahydro-1,4-oxazine (Fluka AG 69880) was repurified by high performance liquid chromatography (HPLC). Spectroscopic grade solvents (carbon tetrachloride, chloroform, cyclohexane, diethyl ether and dichloromethane) were used (Merck Uvasol) without further purification. Their very low water content (max. 0.001%) did not affect complex formation.

Solutions of iodine at around 10^{-4} M were prepared gravimetrically. The solutions of morpholine were made up by accurate dilution of stock solutions prepared gravimetrically. The reactions were carried out directly in spectrophotometer sample cells (quartz, 10 mm optical path length) by mixing 1.5 ml of the morpholine solution in a given solvent with 1.5 ml of a solution of iodine in the same solvent. The absorbances of the solutions were recorded immediately at different wavelengths after mixing with a Kontron 860 UV/Vis spectrophotometer equipped with a Peltier effect thermostated sample holder (temperature regulated to ± 0.1 °C). The temperature of the solutions was kept at 20 ± 0.1 °C throughout the measurements. Formation constants K_c and molar extinction coefficients ε_c were derived from Eq. 1:

$$K_c = \frac{[C]}{([A_0]-[C])([D_0]-[C])} \qquad (1)$$

at the wavelength under investigation: [C] is the concentration of complex, $[A_0]$ is the initial acceptor concentration and $[D_0]$ the initial donor concentration. The term [C] of Eq. 1 can be replaced by d_c/ε_c giving Eq. 2:

$$[A_0][D_0]/d_c = ([A_0]+[D_0]-d_c/\varepsilon_c)/\varepsilon_c + 1/K_c\varepsilon_c \qquad (2)$$

where d_c is the absorbance, ε_0 is the molar extinction coefficient, and K_c the formation constant of the complex. The various parameters were calculated on an Apple IIc computer using a purpose-designed program.

Results

Visible Region At concentrations ranging from 2.10^{-4} and 2.10^{-3} M, morpholine displayed no absorbance between 350 and 600 nm in any of the solvents tested. Addition of a solution of iodine to a solution of morpholine in the same solvent shifted the visible region of the iodine band towards shorter wavelengths. This was attributed to formation of a halogen complex (Fig. 1). The intensity of this new band was found to increase with increasing morpholine concentration at any given concentration of iodine. The spectra crossed at isobestic points between 450 and 470 nm depending on the solvent. The absorption peak of the complex was measured by placing a solution of iodine at the same concentration in the reference beam. The various spectral parameters are shown in Table I.

The stability of the solutions was tested by recording spectra every 5 min. Rapid changes were observed within the first few minutes. Complex formation probably took

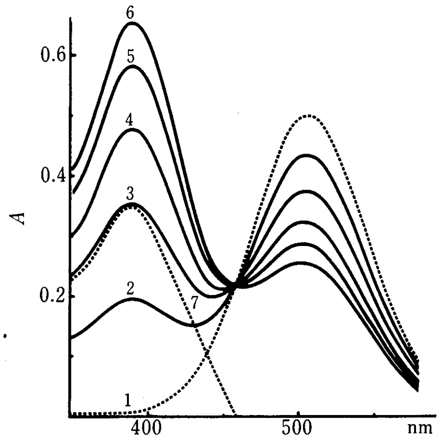

Fig. 1. Visible Spectra of Morpholine–Iodine Complex in $CHCl_3$ at 20 ± 0.1 °C (Quartz Cells with 1 cm Optical Path Length)

Iodine concentration was constant at 5.948×10^{-4} M. Molar concentrations of morpholine are: (1) 0; (2) 2.180×10^{-4}; (3) 4.361×10^{-4}; (4) 6.542×10^{-4}; (5) 8.723×10^{-4}; (6) 1.090×10^{-3}; (7) calculated absorption band in visible region for solution 3.

TABLE I. Principal Spectral Parameters of the Morpholine–Iodine Complex in Various Solvents at 20 ± 0.1 °C

Solvent	Isobestic point (nm)	Absorption peak (nm)	Peak of CTB (nm)
Cyclohexane	470	410	261
CCl_4	470	410	268
Ether	440	390	270
$CHCl_3$	458	390	264
CH_2Cl_2	450	390	265
$CHCl_3 + CCl_4$	460	390	220

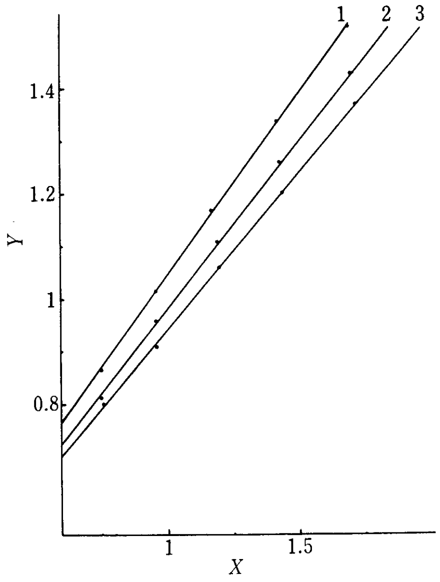

Fig. 2. Relationship between $[I_2][D]/d_c$ and $[I_2]+[D]-d_c/\varepsilon_c$ for the Morpholine–Iodine Complex at 20 °C (CCl_4 Quartz Cells with 1 cm Optical Path Length)

$$Y=\frac{[I_2][D]}{d_c}. \qquad X=[I_2]+[D]-\frac{d_c}{\varepsilon_c}.$$

The regression lines are from equations:
(1) 425 nm $Y=7.001\times10^{-4}$ $X=3.452\times10^{-7}$ ($r=0.999$).
(2) 420 nm $Y=6.369\times10^{-4}$ $X=3.441\times10^{-7}$ ($r=0.999$).
(3) 415 nm $Y=5.913\times10^{-4}$ $X=3.524\times10^{-7}$ ($r=0.999$).

Table II. Formation Constants (K_c) and Molar Extinction Coefficients (ε_c) for Morpholine/Iodine Complexes in Various Solvents

Solvent	λ (nm)	ε_c ($M^{-1}\cdot cm^{-1}$)	K_c (M^{-1})	Mean K_c
Cyclohexane[a)]	415	1558	1716	1735±21
	420	1528	1740	
	425	1475	1722	
	430	1372	1763	
CCl_4[b)]	405	1990	1256	1261±12
	410	2014	1253	
	415	1975	1256	
	420	1873	1280	
Diethyl ether[c)]	405	2477	1571	1388±14
	410	2396	1401	
	415	2164	1349	
	420	1942	1231	
$CHCl_3$[d)]	405	2141	1050	1027±20
	410	2023	1019	
	415	1824	1035	
	420	1647	1002	
CH_2Cl_2[e)]	400	2903	1747	1781±37
	405	2776	1751	
	410	2597	1819	
	415	2455	1807	

Five different solutions of the morpholine–iodine complex were tested in each solvent. The iodine concentration was constant at 5.90×10^{-4} M. The concentrations of morpholine were: *a*) From 2.06×10^{-4} to 1.03×10^{-3} M. *b*) From 2.75×10^{-4} to 1.39×10^{-3} M. *c*) From 1.67×10^{-4} to 8.37×10^{-4} M. *d*) From 2.18×10^{-4} to 1.09×10^{-3} M. *e*) From 2.22×10^{-4} to 1.11×10^{-3} M.

place *via* irreversible reactions. In addition, the appearance of absorption bands between 290 and 360 nm indicated formation of I_3^-. Thermodynamic parameters could not be determined for the morpholine–iodine complex due to its relative lack of stability. For this complex, 1 : 1 stoichiometry was confirmed by mathematical analysis of the π_g–σ_u orbital transition of iodine, analysis of the absorbances, the presence of a single isobestic point, and the exact fit of the experimental points to a linear regression equation (Fig. 2). Further analysis using the Liptay matrix method[7)] also demonstrated the presence of a single complex.

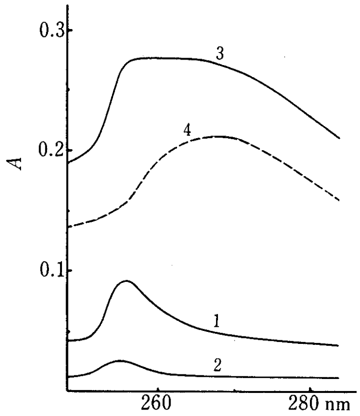

Fig. 3. UV Spectra of Morpholine–Iodine Complex in CCl_4 at 20±0.1 °C (Quartz Cells with 1 cm Optical Path Length)

The molar concentration were: (1) I_2 6.336×10^{-4}; (2) morpholine 1.262×10^{-4}; (3) I_2 6.336×10^{-4} and morpholine 1.262×10^{-5}; (4) calculated absorption band for the complex.

The formation constants K_c and the molar extinction coefficients of the morpholine–iodine complexes are shown in Table II. The values of K_c ranged between 900 and 1.800 mol^{-1} for the various solvents employed.

Ultraviolet (UV) Region In the range of concentrations used (10^{-5} to 10^{-4} M), morpholine exhibited little absorption in the UV for all solvents tested. The formation of a morpholine–iodine complex was indicated by the appearance of a new absorption band, the charge transfer band (CTB). This band was visualised by placing a solution of morpholine at the same concentration in the reference beam. It was quantified by subtracting the absorbance due to the free iodine. The charge transfer band of such complexes has its own characteristic peak in a given solvent. A typical spectrum is shown in Fig. 3. The peaks were all situated between 261 and 270 nm (*cf.* Table I) depending on the solvent. Unfortunately, both iodine and morpholine absorb in this region. This effctively ruled out determination of the ionisation potential of morpholine by spectroscopic methods.

Conclusion

Spectroscopic analysis of the charge transfer complexes of morpholine with iodine demonstrated their *n*-σ character. The results indicated strong donor–acceptor interactions. However, the values of K_c are considerably less than those reported for other simple heterocyclic compounds (*cf.* Table III). This can be explained by the lack of aromatic character of morpholine, in contrast to the 8 compounds listed in Table III. The nature of the solvent has a marked influence on the values of K_c ($CHCl_3$: $K_c=1034\,M^{-1}$; CH_2Cl_2: 1781 M^{-1}). We found no relationship between the values of K_c and the polarity of the solvent. The morpholine–iodine complex is formed in a two stage reaction. An "external complex," morpholine–I–I is formed rapidly. This slowly

TABLE III. Formation Constants K_c of Iodine Complexes with Various Heterocyclic Compounds

Solvent	Compound	K_c (M^{-1})	Temp. (°C)
CH_2Cl_2	Pyridine[a]	175.4	20
	Pyridazine[a]	31.8	20
	Pyrimidine[a]	12.3	20
	Pyrazine[a]	7.1	20
n-Heptane	Thiophen[b]	0.59	20
	Furan[b]	0.20	20.5
	Pyrrole[b]	6.50	21
CCl_4	Thiazole[c]	10.3	20

a) Ref. 1. *b*) Ref. 2. *c*) Ref. 3.

changes to an "internal complex" [morpholine I^+]I^-. The I^- ions liberated react with excess I_2 to form I_3^- ions which were always detected in solutions of the complex.

$$\text{morpholine} + I_2 \rightleftarrows \text{morpholine–I–I}$$

$$\text{morpholine–I–I} \rightleftarrows \text{morpholine–}I^+I^-$$

$$\text{morpholine–}I^+I \rightleftarrows [\text{morpholine–I}]^+ + I^-$$

$$I^- + I_2 \rightleftarrows I_3^-$$

Previous work from our laboratory[4,6] has demonstrated that antithyroid activity can be expected from molecules whose formation constant of the iodinated complex K_c exceeds $100\,\mathrm{M}^{-1}$. Above this value, anti-thyroid activity is directly related to the value of this constant. For morpholine we found a value of around $1.500\,\mathrm{M}^{-1}$, and this compound could therefore be suspected to interfere with thyroid function. This result has two main implications: Molecules containing a morpholine nucleus may form charge transfer complexes with iodine, and thus have anti-thyroid activity. Thyroid dysfunction may be a side effect of treatment with such drugs. Morpholine could serve as a starting point for the synthesis of novel antithyroid agents.

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