Chem. Pharm Bull. **37**(8) 2248—2250 (1989) Vol. 37, No. 8

Charge-Transfer Complexes between Linear Methyl Sulfides and Iodine

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Received December 26, 1988

Charge-transfer complexes between linear methyl thioethers R–S–CH_3 (R = Me, Et, Pr, Bu and $C_{10}H_{21}$) and iodine in solution in carbon tetrachloride were studied by ultraviolet/visible spectroscopy at various temperatures. The spectral and thermodynamic parameters indicated a high stability of the complexes, and a +I inductive effect of the alkyl substituents on the mobility of the *n* electron of the sulfur. The values of the formation constants of the iodinated complexes for the thioethers range from 94.6 to 149 M^{-1} at 20 °C, significantly higher than those for complexes formed between iodine and the corresponding thiols and disulfides. These results suggest that substitution of the sulfur atom in antithyroid drugs of the R-SH type (*e.g.*, methimazole) might enhance their activity.

Keywords alkyl sulfide; charge-transfer complex; iodine; antithyroid agent

The mode of action of synthetic antithyroid agents (SATs) is not well understood, although two main possibilities have been proposed, one enzymatic[1] and the other purely chemical.[2,3] We have studied the mechanism of action based on a chemical interaction between synthetic antithyroid drugs (tetramethylthiourea, 2-mercapto-1-methylimidazole, 2-thiazoline-2-thiol) and molecular iodine. These compounds are thought to react with iodine to form a charge-transfer complex of the n–σ type with essentially 1 : 1 stoichiometry. The values of the formation constants K_c of the iodinated complexes indicate that these compounds are strong electron donors.[4] All the current antithyroid agents contain a non-cyclic sulfur atom, and it has been found that the higher the electron donor action the higher is the antithyroid activity. In the course of a systematic investigation of new agents with potential thyroid activity, and in line with previously established structure–activity relationships, we therefore investigated the formation of molecular complexes of iodine with various linear methyl sulfides.

There have been a number of reports of charge-transfer complexation parameters between organic sulfides and iodine.[5-8] However, there has been relatively little work on the complexes between linear methyl sulfides and iodine. Tideswell *et al.*[9] carried out a study by visible spectroscopy, while Strom *et al.*[10] used proton nuclear magnetic resonance (^{1}H-NMR) methods to determine values of K_c for the complexes of iodine with methyl and ethyl thioethers. However, there is considerable dispersion in the values obtained from these studies. For our work on structure–activity relationships of SATs, we required a strictly comparable set of values for a given series. This was the main rationale for studying this series of linear methyl sulfides under strictly controlled conditions.

Experimental

Materials The following thioethers were investigated: CH_3–S–CH_3 (Me_2S), CH_3–S–C_2H_5 (Me–S–Et), CH_3–S–$(CH_2)_2$–CH_3 (Me–S–*n*Pr), CH_3–S–$(CH_2)_3$–CH_3 (Me–S–*n*Bu) and CH_3–S–$(CH_2)_9$–CH_3 (Me–S–*n*De). These linear methyl sulfides were prepared by alkylation of the corresponding thiol in a slight excess of methyl iodide in alkaline conditions under an atmosphere of nitrogen. The sulfides were recovered by fractional distillation (under reduced pressure when necessary), and purified by preparative gas phase chromatography (Varian 920; aluminum column 3/8″ × 6 m long; Chromosorb WAW 45/60 impregnated with 20% SE 30 silicone; vector gas = hydrogen 40 ml/min). The identity and purity of the sulfides were confirmed by infrared (IR) spectroscopy and analytic gas liquid chromatopraphy (GLC). Iodine was bisublimed (Merck Ultrapur 4763) and was employed without further purification. It was kept in a desiccator containing P_2O_5. Carbon tetrachloride was of spectroscopic grade (Merck Uvasol 2209), and was used without further purification. Its low water content (max. 0.005%) did not affect the formation of the iodinated complexes.

Procedure The solutions of the donors (methyl sulfides) and acceptor (iodine) in carbon tetrachloride were prepared by dilution of stock solutions made up by accurate weighing. The complexes were formed directly in quartz sample cuvettes (1 cm optical path length) by mixing 1.5 ml of a solution of methyl sulfide and 1.5 ml of a solution of iodine. Before mixing, the cuvettes were carefully dried in a stream of nitrogen.

The ultraviolet (UV) and visible spectra were recorded on a UVIKON 930 spectrophotometer equipped with a thermostated sample holder (±0.1 °C).

The formation constants of the complexes were calculated by a previously described method[11] using a Mini 6 computer at the Limoges University Computing Center.

Results

The methyl sulfide R–S–CH_3 are transparent between 700 and 300 nm in solution in carbon tetrachloride at around 10^{-2} M. In the same solvent, the acceptor I_2 has two absorption bands, one in the visible region at 515 nm ($\log_{10}\varepsilon = 2.96$), the other in the near UV region at 280 nm ($\log_{10}\varepsilon = 1.84$). Mixing of solutions of the thioether and the halogen leads to a modification of the spectrum.

Visible Spectrum There is a hypsochromic shift (blueshift) from the $\pi_g \rightarrow \sigma_u$ of iodine. The spectra recorded at various concentrations cross at a single isosbestic point. By subtracting the absorption of the free iodine from that of the complexes, the visible band of the complex could be determined accurately (Fig. 1, curve 7).

UV Spectrum The solutions of the complexes display a new absorption band (Fig. 2, curve 3) which was attributed to charge-transfer of the n–σ type. The peak of this charge-transfer band (CTB: 301 nm for Me_2S, 305 nm for the other sulfides) was obtained by subtraction of the slight absorption of iodine at this wavelength from the absorption of curve 3.

The absorption at 290—305 nm is particularly intense. It is possible that the charge-transfer bands were affected by a band at 290 nm due to I_3^- ions formed by the following mechanism[12]:

$$RSR' + I_2 \rightleftharpoons RSR' - I_2 \qquad \text{(outer complex)}$$

$$RSR' - I_2 \rightleftharpoons RSR' - I^+I^-$$

$$RSR' - I^+I^- \rightleftharpoons [RSR' - I]^+ + I^- \qquad \text{(inner complex)}$$

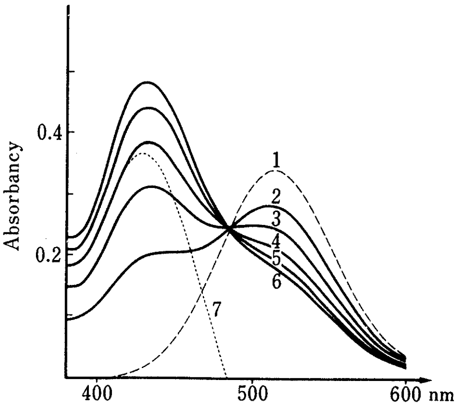

Fig. 1. Visible Absorption Spectra of a Solution of a Mixture of Me–S–*n*Pr and I_2 (3.72×10^{-4} M) in CCl_4 (10 mm Optical Path Length, $\theta = 20.0$ °C)

The concentrations of donor are ($\times 10^{-2}$ M): 1) 0, 2) 0.233, 3) 0.467, 4) 0.700, 5) 0.934, 6) 1.167. The absorption band in the visible region was measured by placing a solution of I_2 in the reference beam (curve 7).

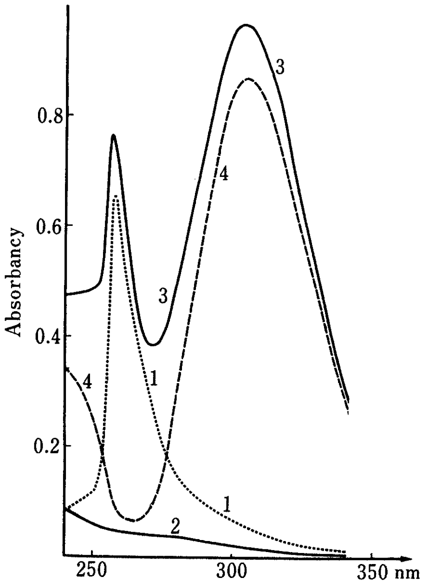

Fig. 2. UV Absorption Spectra of a Solution of a Mixture of Me–S–*n*Pr and I_2 in CCl_4 (10 mm Optical Path Length, $\theta = 20.0$ °C)

The concentrations of donor are ($\times 10^{-4}$ M): 1) Me–S–*n*Pr, 7.00; 2) I_2, 3.72; 3) Me–S–*n*Pr, 7.00 and I_2, 3.72; 4) UV absorption band (charge-transfer band) is obtained by subtracting the absorption due to free donor and acceptor.

Table I. Equilibrium Constants K_c and Molar Extinction Coefficients ε_c of the Iodine Complexes[a] of Thioethers in Solution in CCl_4 at 20 ± 0.1 °C

Donor	λ (nm)	ε_c ($\times 10^3$) ($M^{-1} cm^{-1}$)	K_c (M^{-1})	$K_c \pm$ mean (M^{-1})
Me–S–Me	420	1.64	94	
	425	1.73	95	
	430	1.80	94	
	435	1.81	95	95 ± 0.49
	440	1.78	95	
	445	1.71	95	
	450	1.60	95	
Me–S–Et	420	1.98	136	
	425	2.10	134	
	430	2.14	136	
	435	2.14	135	135 ± 0.90
	440	2.09	134	
	445	1.98	135	
	450	1.83	134	
Me–S–*n*Pr	420	1.91	142	
	425	2.01	141	
	430	2.06	142	
	435	2.06	141	141 ± 0.53
	440	2.00	141	
	445	1.90	141	
	450	1.76	142	
Me–S–*n*Bu	420	2.06	143	
	425	2.15	144	
	430	2.20	144	
	435	2.19	144	144 ± 0.97
	440	2.13	145	
	445	2.01	145	
	450	1.86	146	
Me–S–*n*De	420	2.08	149	
	425	2.18	148	
	430	2.23	148	
	435	2.22	149	149 ± 0.90
	440	2.15	150	
	445	2.04	148	
	450	1.87	150	

a) The values of K_c and ε_c were calculated from solutions of the complex $RSCH_3$–I_2 at five different concentrations.

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

The presence of I_3^- ions in the solutions of the complex meant that we were unable to calculate the extinction coefficients from the wavelength at the peak of the CTB.

Stoichiometry Literature data[6,7] and our own observations indicate that the complexes of the alkyl sulfides with iodine

$$R\text{–}S\text{–}R' + I_2 \rightleftharpoons RSR' - I_2$$

are of 1 : 1 stoichiometry, which was confirmed by the exact fit of the experimental points on a linear regression line, and the single isosbestic point. This is in agreement with crystallographic studies[13] which have demonstrated that the S–I–I atoms are colinear.

The results listed in Tables I and II demonstrate the strong interaction between iodine and these thioethers.

Stability These complexes were found to be highly stable, since identical results were obtained from measurements carried out 24 and 48 h after mixing. According to the theory of Mulliken, the stability of charge-transfer complexes is proportional to:

– the hypsochromic shift $\Delta\lambda$ of the visible band of iodine. This was relatively high for the thioethers tested ($\Delta\lambda = 84$ nm). The values of $\Delta\lambda$ for organic thiocyanates range from 50—60 nm,[14] and from 60—65 nm for the isothiocyanates.[15]

– the absolute value of the change in enthalpy of the complexes $|\Delta H°|$, which ranged from 7—8 kcal/mol (Table II). It has been shown that charge-transfer complexes of the *n*–σ type are highly stable if $|\Delta H°|$ lies between 3 and 12 kcal/mol.[16]

Influence of the Group R on the Basicity of the Donor The basicity of the *n* donor sulfur derivatives lies between that of the corresponding oxygen and nitrogen derivatives.[6] This basic character depends partly on the inductive donor effect (+I) of the alkyl groups attached to the sulfur. The values of K_c obtained can be used to define the basicity of the thioethers, which were found to increase with increasing +I in the following order:

TABLE II. Equilibrium Constants K_c at Various Temperatures and Thermodynamic Parameters of the $RSCH_3$–I_2 Complexes in Solution in CCl_4

Donor	θ (°C)	K_c (M^{-1})	$-\Delta H^\circ$ (k cal/mol) $-\Delta S^\circ$ (e.u.) $-\Delta G^\circ_{293K}$ (k cal/mol)
Me–S–Me[a]	5	203 ± 0.52	
	10	155 ± 0.76	8.3 ± 0.1
	15	120 ± 0.70	
	20	95 ± 0.49	19.4 ± 0.3
	25	74 ± 0.49	
	30	58 ± 0.63	2.6 ± 0.2
Me–S–Et	10	206 ± 0.71	
	15	164 ± 0.67	7.3 ± 0.1
	20	135 ± 0.90	
	25	107 ± 0.49	15.4 ± 0.4
	30	83 ± 0.56	
	35	72 ± 0.63	2.9 ± 0.2
	40	60 ± 0.74	
Me–S–*n*Pr	10	232 ± 1.02	
	15	180 ± 0.57	8.2 ± 0.2
	20	141 ± 0.53	
	25	112 ± 0.75	18.1 ± 0.5
	30	89 ± 0.87	
	35	71 ± 0.87	2.9 ± 0.3
	40	58 ± 0.90	
Me–S–*n*Bu	10	226 ± 0.78	
	15	178 ± 0.93	7.7 ± 0.2
	20	144 ± 0.97	
	25	115 ± 0.37	16.4 ± 0.6
	30	91 ± 1.27	
	35	76 ± 1.14	2.9 ± 0.3
	40	63 ± 1.50	
Me-S-*n*De	10	234 ± 1.46	
	15	186 ± 0.78	7.6 ± 0.3
	20	149 ± 0.90	
	25	120 ± 1.11	16.0 ± 1.0
	30	97 ± 2.05	
	35	80 ± 1.81	2.9 ± 0.6
	40	66 ± 3.47	

a) In view of the low boiling point ($bp_{760} = 37.3$ °C) of Me–S–Me, measurements were only carried out at 6 temperatures for this compound.

$$\text{Me} \ll \text{Et} < n\text{Pr} < n\text{Bu} < n\text{De}$$

However, there was only a slight increase in basicity for linear alkyl groups containing more than 4 carbons.

The Taft constants σ_I were too close together for the alkyl groups with more than 2 carbons to establish a linear relationship between ΔH° and the sum of the constants σ_I of the inductive effect of the substituents.[17] In fact, the values of the differences of standard enthalpies and entropies for equilibria of complexation did not change monotonically with increasing chain length. This anomaly indicated that complexation is sensitive to non-polar factors, possibly involving steric hindrance.

Conclusion

The charge-transfer complexes formed between methyl thioethers and iodine were found to be of the n–σ type with a 1 : 1 stoichiometry. In order to establish structure–activity relationships for potential antithyroid agents, we compared the donor properties of these thioethers with literature data on homologous series of thiols, sulfides and disulfides. The values of the formation constants K_c of the iodinated complexes of the methyl sulfides showed that these compounds are in fact stronger donors than either the thiols R–SH or disulfides R–S–S–R′.[6,18,19]

In previous studies, we showed that the antithyroid activity of a compound is directly related to its electron donor power, and that this can be quantitated from the formation constant of the iodinated complex.[2,3] For example, 2-mercapto-1-methylimidazole, one of the most powerful antithyroid agents known, has a K_c value of $2.31 \times 10^4 \pm 667\ M^{-1}$ ($\theta = 20$ °C, CCl_4).[20] On the basis of the results reported here, the K_c value of the complex of iodine with 1-methylimidazole-2-thiol could probably be increased by alkylation of the thiol group with a methyl, ethyl or *n*-propyl group.

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