UV-Visible, IR, and ^{13}C NMR Studies on CT Complexes between Some Thiohydantoins and Molecular Diiodine

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ABSTRACT

The reaction of some 5,5-dimethyl-2-thiohydantoin derivatives $\overline{RNC(Me)_2CXNR'CS}$ (X = O, S; R, R' = H, Me) with molecular diiodine has been studied in CH_2Cl_2 solution by different spectroscopic techniques. The formation constants (K) of the 1:1 molecular adducts and their thermodynamic parameters have been measured by UV-visible spectroscopy. The results allow us to point out the different donor properties of C(2) = S thioketonic sulfur between the two series of compounds (X = O, S) and the influence of N(1) and N(3) methylation on the K's. From the analysis of the ν(NH) frequencies, it has been possible to show hydrogen bond interactions between the NH's and the S-bonded iodine; this seems to be an important factor in determining the K values.

INTRODUCTION

During past years, we have carried out systematic studies on the interaction of organic molecules of biological interest with molecular diiodine [1–6]. The donors considered in these studies were pentaatomic rings like pyrrolidines, oxazolidines, thiazolidines, imidazolidines and their benzo-derivatives, and, more recently, hydantoins containing at least one thio- or seleno-amido group.

Our main interest was the evaluation of the formation constant K of the 1:1 adduct, according to the following reaction:

$$D + I_2 \rightleftharpoons D \cdot I_2 \qquad (1)$$
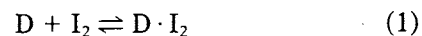
where D is the donor molecule and $D \cdot I_2$ its charge-transfer complex with diiodine.

These studies were first stimulated by the importance that compounds containing thioketonic sulfur have in the treatment of pathologies of the thyroid, since they are able to pick up diiodine selectively during the oxidation process of I^- to I radical or I^+ cation by means of the enzyme, thyroid peroxydase [7].

In this article, we will report the results of the determination of the K's and the thermodynamic parameters of Reaction 1 for compounds **1**, **2**, and **4** and compare them with the results obtained for compounds **3**, **5**, **6**, **7**, and **8** reported in a previous article [6].
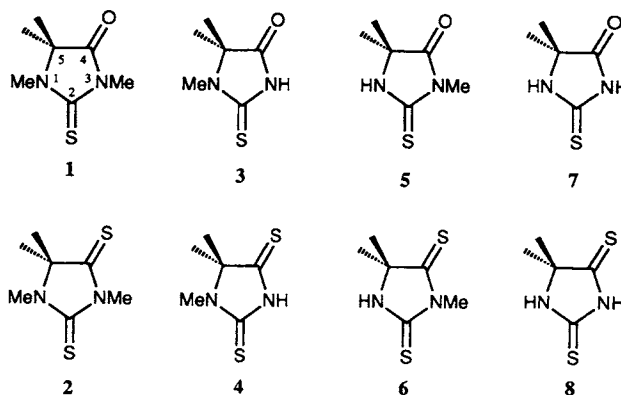
TABLE 1 UV Absorption (nm) (Log ϵ in Parentheses) of the Free Molecules and Isosbestic Points (nm) Obtained between the I_2 Visible Band and Its Blue-Shifted Band (CH_2Cl_2 Solutions)

Compound	UV Absorptions	Isosbestic Points	Reference
1	238 (4.14) 265 (4.23) 305 (2.13)	498	this work
2	301 (4.09) 387 (1.74)	500	this work
3	266 (4.25) 297 (3.48) 378sh (0.95)	483	6
4	299 (4.48) 388 (1.68)	487	this work
5	266 (4.32) 304 (2.95)	476	6
6	303 (4.51) 392 (1.80)	463	6
7	266 (4.34) 305 (2.28)	481	5
8	299 (4.46) 394 (1.69)	481	5

TABLE 2 Molar Extinction Coefficients (ϵ) at the Wavelengths (λ) Used for the Calculation, Association Constants (K), Ranges of the Saturation Fraction (s), and Sum of the Squared Deviations (χ^2) for Reaction between Compound 1 and I_2 (Standard Deviations in Parentheses)

t ($°C$)	λ (nm)	ϵ ($dm^3\ mol^{-1}\ cm^{-1}$)	K ($dm^3\ mol^{-1}$)	s^a	χ^2
15	360	14,780 (60)	46.4 (1.0)	0.055 ÷ 0.474	0.016
	350	24,090 (91)			
	340	33,440 (120)			
	330	35,500 (162)			
20	360	14,550 (63)	39.3 (0.9)	0.047 ÷ 0.433	0.011
	350	23,610 (88)			
	340	32,700 (118)			
	330	34,740 (141)			
25	360	15,380 (56)	30.9 (1.4)	0.038 ÷ 0.376	0.086
	350	24,750 (69)			
	340	33,470 (183)			
	330	34,900 (359)			
30	360	15,290 (65)	26.3 (0.9)	0.032 ÷ 0.339	0.027
	350	24,510 (90)			
	340	33,490 (122)			
	330	35,660 (201)			
35	360	15,270 (58)	22.6 (0.6)	0.028 ÷ 0.305	0.010
	350	24,210 (69)			
	340	33,270 (77)			
	330	35,560 (142)			

$\Delta H = -27(1)$ kJ·mol^{-1}; $\Delta S = -63(4)$ J·mol^{-1}·K^{-1}; and $r^b = 0.998$.

[a]In this case, the saturation fraction (s) is defined as the ratio between the concentration of the adduct and the analytical concentration of the donor.
[b]Correlation coefficient of the plot ln K vs. $1/T^\circ$.

EXPERIMENTAL

Materials

1,5,5-Trimethyl-4-oxoimidazolidine-2-thione (3), 3,5,5-trimethyl-4-oxoimidazolidine-2-thione (5), 3,5,5-trimethylimidazolidine-2,4-dithione (6), 5,5-dimethyl-4-oxoimidazolidine-2-thione (7), and 5,5-dimethylimidazolidine-2,4-dithione (8) have been prepared according to the literature [6,8,9,10]. Diiodine was purified by sublimation from KI and stored in a desiccator.

1,3,5,5-Tetramethyl-4-oxoimidazolidine-2-thione (1)

A mixture of 1,3,5,5-tetramethylimidazolidine-2,4-dithione (2) (1.1 g, 5.8 mmol), $HgCl_2$ (1.6 g, 5.8 mmol), and 10% HCl (55 mL) was refluxed for 84 hours. The reaction mixture was then filtered to eliminate HgS, and the filtrate was extracted with $CHCl_3$. The organic extract was washed with water until neutrality had been achieved and then dried and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, using $CHCl_3$ as eluant, to give 1 (0.5 g, 50% yield). This compound, which was homogeneous to TLC analyses, had the following. Mp: 153–155°C. IR (KBr): ν 2988 (m), 2950 (m), 2870 (m), 1745 (s), 1510 (s), 1475 (m), 1450 (m), 1430 (m), 1408 (m), 1390 (m), 1375 (m), 1355 (s), 1340 (s), 1295 (w), 1245 (w), 1170 (m), 1135 (s), 1065 (s), 972 (s), 950 (w), 860 (m), 830 (m), 755 (m), 645 (m), 568 (s), 490 (s), 440 (w), 355 (w) cm^{-1}. Anal., calcd for $C_7H_{12}N_2OS$,

TABLE 3 Molar Extinction Coefficients (ϵ) at the Wavelengths (λ) Used for the Calculation, Association Constants (K), Ranges of the Saturation Fraction (s), and Sum of the Squared Deviations (χ^2) for Reaction between Compound **2** and I_2 (Standard Deviations in Parentheses)

t (°C)	λ (nm)	ϵ (dm^3 mol^{-1} cm^{-1})	K (dm^3 mol^{-1})	s^a	χ^2
15	420	2502 (30)	24.7 (0.2)	0.039 ÷ 0.384	0.041
	405	2991 (37)			
	390	5574 (84)			
	375	13,140 (126)			
20	420	2495 (25)	21.3 (0.2)	0.034 ÷ 0.350	0.029
	405	3004 (38)			
	390	5567 (80)			
	375	13,030 (120)			
25	420	2428 (23)	19.1 (0.2)	0.031 ÷ 0.325	0.022
	405	2933 (39)			
	390	5394 (73)			
	375	12,550 (116)			
30	420	2341 (26)	17.4 (0.2)	0.028 ÷ 0.305	0.017
	405	2832 (39)			
	390	5158 (65)			
	375	11,940 (111)			
35	420	2391 (35)	15.0 (0.2)	0.024 ÷ 0.274	0.015
	405	2894 (42)			
	390	5118 (82)			
	375	11,970 (108)			

$\Delta H = -17.7(0.8)$ kJ·mol^{-1}; $\Delta S = -35(3)$ J·mol^{-1}·K^{-1}; and $r^b = 0.997$.

[a] In this case, the saturation fraction (s) is defined as the ratio between the concentration of the adduct and the analytical concentration of the donor.
[b] Correlation coefficient of the plot ln K vs. $1/T°$.

TABLE 4 Molar Extinction Coefficients (ϵ) at the Wavelengths (λ) Used for the Calculation, Association Constants (K). Ranges of the Saturation Fraction (s), and Sum of the Squared Deviations (χ^2) for Reaction between Compound **4** and I_2 (Standard Deviation in Parentheses)

t (°C)	λ (nm)	ϵ (dm^3 mol^{-1} cm^{-1})	K (dm^3 mol^{-1})	s^a	χ^2
15	420	2456 (10)	190 (5)	0.234 ÷ 0.790	0.019
	400	2281 (15)			
	380	3101 (24)			
	370	4835 (25)			
20	420	2368 (10)	156 (4)	0.205 ÷ 0.755	0.014
	400	2219 (14)			
	380	3085 (22)			
	370	4829 (24)			
25	420	2264 (11)	131 (4)	0.182 ÷ 0.722	0.011
	400	2142 (15)			
	380	3041 (21)			
	370	4781 (24)			
30	420	2128 (13)	114 (4)	0.164 ÷ 0.693	0.010
	400	2035 (15)			
	380	2947 (21)			
	370	4651 (26)			
35	420	2021 (17)	97 (5)	0.145 ÷ 0.658	0.017
	400	2041 (37)			
	380	2891 (23)			
	370	4581 (30)			

$\Delta H = -24.5 (0.7)$ kJ·mol^{-1}; $\Delta S = -42(2)$ J·mol^{-1}·K^{-1}; and $r^b = 0.999$.

[a] In this case, the saturation fraction (s) is defined as the ratio between the concentration of the adduct and the analytical concentration of the donor.
[b] Correlation coefficient of the plot ln K vs. $1/T°$.

TABLE 5 Interpolated Stability Constants K ($dm^3 \cdot mol^{-1}$; 25°C; CH_2Cl_2 Solutions) and Thermodynamic Parameters ΔH ($kJ \cdot mol^{-1}$) and ΔS ($J \cdot mol^{-1} \cdot K^{-1}$) of the 1:1 Adducts between Molecular Diiodine and **1–8**

Compound	K	$-\Delta H$	$-\Delta S$	Reference
1	32	27	63	this work
2	19	17.7	35	this work
3	149[a]	22	32	6
4[b]	132	24.5	42	this work
5	171[a]	31	62	6
6	126[a]	27	49	6
7	201[a]	33	67	5
8	143[a]	30	58	5

[a]These values have been interpolated between those obtained at 17°C and 35°C; obviously the relative thermodynamic parameters are only indicative, so they are given without standard deviations. [b]The K's of this compound have been redetermined, since they do not fit the other values depicted in Table 5, being clearly underestimated [6].

found (%): C (48.8) 48.9; H (7.0) 7.3; N (16.3) 16.7; S (18.6) 18.2.

1,3,5,5-Tetramethylimidazolidine-2,4-dithione (2)

A mixture of 1,3,5,5-tetramethylimidazolidine-2,4-dione [11] (1 g, 6.4 mmol), P_2S_5 (0.91 g, 4.11 mmol) in 20 mL of 1,2,3,4-tetrahydronaphthalene was refluxed for 2 hours and then filtered while still warm. The filtrate was treated with hexane until it became turbid, and it was then kept for some hours at 4°C. The yellow solid obtained by filtration was purified by flash chromatography on silica gel, using CHCl₃ as eluant, to give **2** (0.31 g, 26% yield).

TABLE 6 Bond Distances (Å) and Angles (°) Related to the NH···I Groups

	3·I₂	7·I₂	8·I₂	8·2I₂
N(1)-H			0.96	0.85	0.94
N(3)-H	1.14			0.98
N(1)-I		3.62	3.60	3.47
N(3)-I	3.55			3.70
N(1)H-I		2.93	3.16	2.90
N(3)H-I	2.79			3.15
<N(1)HI		129.7	114.3	120.6
<N(3)HI	123.9			117.5
Reference	17	18	18	18
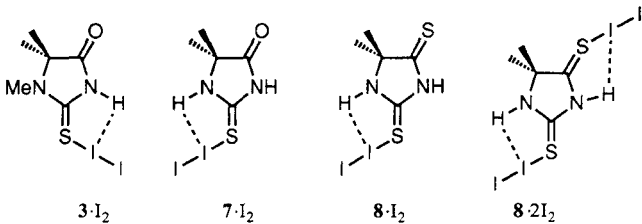
TABLE 7 v (NH) Stretching Vibrations (cm^{-1}) of N(1)H and N(3)H Groups for the Free Ligands, Their Adducts with I_2, and Relative Shifts Δv (NH) (= v (NH)$_{free\ ligand}$ − v(NH)$_{adduct}$) (CH_2Cl_2 solutions)

	v (NH)$_{free\ ligand}$		v (NH)$_{adduct}$		Δv (NH)		
Compound	N(1)	N(3)	N(1)	N(3)	N(1)	N(3)	Reference
3		3420		3375		45	this work
4		3397		3364		33	this work
5	3437		3385		52		15
6	3430		3373		57		15
7	3431	3405	3373	3345	58	60	this work
8	3435	3405	3374	3341	61	64	this work

This compound, which was homogeneous to TLC analyses, had the following. Mp 151–153°C. IR (KBr): v 2982 (m), 2940 (m), 1515 (s), 1465 (m), 1432 (s), 1405 (m), 1385 (m), 1370 (s), 1320 (s), 1302 (s), 1194 (w), 1180 (w), 1160 (w), 1108 (m), 1055 (m), 1010 (m), 965 (m), 940 (w), 822 (m), 760 (m), 632 (w), 518 (m), 435 (m) cm^{-1}. Anal., calcd for $C_7H_{12}N_2S_2$, found (%): C (44.7) 44.9; H (6.4) 6.5; N (14.9) 15.0; S (34.0) 34.0.

1,5,5-Trimethylimidazolidine-2,4-dithione (4)

This compound was synthesized following the same procedure described for **2** and using 1,5,5-trimethylimidazolidine-2,4-dione [11] (1 g, 7 mmol) as starting material. The chemically pure **4** (TLC analyses) (0.97 g, 79.5% yield) had the following. Mp 145–148°C. IR (KBr): v 3100 (m br), 3060 (m), 2982 (m), 2965 (m), 2895 (m), 1635 (w), 1535 (s), 1470 (s), 1450 (s), 1440 (s), 1400 (s), 1390 (m), 1380 (m), 1360 (m), 1340 (w), 1300 (s), 1245 (s), 1185 (m), 1160 (s), 1080 (s), 970 (m), 940 (w), 885 (m), 785 (m br), 752 (m), 695 (m), 685 (w), 643 (m), 570 (m), 505 (s), 445 (s), 435 (m) cm^{-1}. Anal., calcd for $C_6H_{10}N_2S_2$, found (%): C (41.4) 41.5; H (5.8) 5.9; N (16.1) 16.3; S (36.8) 36.8.

Spectrophotometric Measurements and Data Treatment

The spectrophotometric measurements were carried out in CH_2Cl_2 solutions by use of a Varian model Cary 5 UV-Vis-NIR spectrophotometer equipped with a temperature controller accessory and connected with an IBM Personal System 2. The spectra of 12 different solutions were recorded in the 300 to 500 nm range at temperatures of 15, 20, 25, 30, and 35°C. The choice of the concentrations of the reagents was made according to the criteria outlined in Ref. [12] and widely discussed in previous articles [13]; however, in all the solutions, the concentration of ligands was always higher than that of diiodine in order to avoid the formation of adducts different from 1:1. Data analysis was car-

TABLE 8 ^{13}C NMR Chemical Shifts (δ) of Compounds **1–8** of the 1:1 CT Complexes and Their Differences $\Delta\delta^0$ (=Chemical Shift of the Adduct-Chemical Shift of the Ligand)

Compound	C(2)	C(4)	C(5)	Me/Me	N(1)Me	N(3)Me
1	181.17	176.87	63.73	21.67	29.06	27.91
1·I$_2$	178.84	176.19	65.15	21.53	30.48	28.76
$\Delta\delta^0$	−2.33	−0.68	1.42	−0.14	1.42	0.85
2	179.54	208.07	74.97	25.95	30.86	33.22
2·I$_2$	177.00	207.62	77.01	25.94	32.30	34.10
$\Delta\delta^0$	−2.54	−0.45	2.04	−0.01	1.44	0.88
3	178.41	176.59	65.63	21.58	28.61	—
3·I$_2$	176.25	174.93	67.06	21.60	29.42	—
$\Delta\delta^0$	−2.16	−1.66	1.43	0.02	0.81	—
4	177.13	208.66	76.99	25.99	29.99	—
4·I$_2$	174.58	207.34	78.79	25.76	30.78	—
$\Delta\delta^0$	−2.55	−1.32	1.80	−0.23	0.79	—
5	182.72	177.06	60.87	23.95	—	27.33
5·I$_2$	180.12	175.96	62.68	23.83	—	27.51
$\Delta\delta^0$	−2.60	−1.10	1.81	−0.12	—	0.18
6	181.39	209.38	71.35	27.98	—	32.24
6·I$_2$	179.20	208.77	73.88	28.10	—	32.35
$\Delta\delta^0$	−2.19	−0.61	2.53	0.12	—	0.11
7	180.30	177.23	63.49	23.85	—	—
7·I$_2$	178.20	175.60	64.92	23.72	—	—
$\Delta\delta^0$	−2.10	−1.63	1.43	−0.13	—	—
8	179.27	210.31	74.35	27.78	—	—
8·I$_2$	177.48	208.91	75.78	27.77	—	—
$\Delta\delta^0$	−1.79	−1.40	1.43	−0.01	—	—

ried out with a program using a nonlinear least-squares method [14], based on the assumption that the best values of K and ϵ are those which minimize the sum of the function $\chi^2 = \Sigma(A_C - A_S)^2/(N - 2)$, where A_c and A_s are the calculated and experimental absorbances and N is the number of data points. The optimization of K was carried out at four different wavelengths.

The infrared spectra were taken in the range of 3600–3100 cm^{-1} in CH$_2$Cl$_2$ solution in an 0.2 cm pathway quartz cell, using a Perkin Elmer 983 instrument connected with a Perkin Elmer 7500 Data Station. The envelopes of the bands due to v (NH) have been deconvoluted with a program which treats every band as a Gaussian curve and minimizes the sum of the squared deviations between the experimental and calculated absorbances.

^{13}C NMR Measurements and Data Treatment

The ^{13}C NMR spectra were recorded at the temperature of 20°C on a Varian FT-NMR spectrometer VXR 300, operating at 75.4 MHz frequency. CDCl$_3$ (77.00 ppm) was employed as the external reference. Several solutions having the concentration of the ligand (2.0 ÷ 3.0 × 10^{-2} mol/dm^3) in CH$_2$Cl$_2$ constant but with increasing amounts of diiodine were recorded. Likewise, the maximum diiodine/donor molar ratio employed was about

3.5 in order to shift the equilibrium reaction toward complex formation.

From equilibrium (1), the ^{13}C NMR observed chemical shift, δ, is given by [15]

$$\delta = \frac{[D]\delta_D^0}{[D]^0} + \frac{[DI_2]\delta_{DI_2}^0}{[D]^0} \tag{2}$$

where $[D]$ and $[DI_2]$ are the equilibrium concentrations of the free donor and the complex, respectively, $[D]^0$ the analytical concentration of the donor, δ_D^0 the measured chemical shifts of the donor, and $\delta_{DI_2}^0$ the complex chemical shift to be evaluated.

From Equation 2,

$$\delta = \delta_D^0 + \frac{\Delta\delta^0[DI_2]}{[D]^0} \tag{3}$$

where $\Delta\delta^0 = \delta_{DI_2}^0 - \delta_D^0$. From the slopes of the straight lines $(\delta - \delta_D^0)$ $[D]^0$ vs. $[DI_2]$, the values of $\Delta\delta^0$ and hence $\delta_{DI_2}^0$ for all the carbons have been calculated.

RESULTS AND DISCUSSION

Although compounds **1–8** have two chalcogen atoms capable of coordinating molecular diiodine, the UV-visible spectrophotometric data in CH$_2$Cl$_2$ solutions fit fairly well the 1:1 model according to Reaction 1 under the experimental conditions used

for the K determinations. The absence of other equilibria besides that leading to the 1:1 model was experimentally verified by the presence of isosbestic points.

Table 1 shows the UV absorption maxima of the free ligands and the isosbestic points obtained between the visible band of diiodine and its blue shifted band due to adduct formation.

As described in previous articles [4,5], for the simultaneous determination of the equilibrium constant (K) and the molar extinction coefficients (ϵ) of $D \cdot I_2$, we have followed the criterion of enlarging the experimental range of the saturation fraction (s [s = adduct concentration to reagent at lowest concentration ratio]) as far as possible, in order to minimize the errors in K and ϵ.

The K and ϵ values with the relative standard deviations calculated at five different temperatures, together with the thermodynamic parameters and the ranges of the saturation fraction for compounds **1**, **2**, and **4** are reported in Tables 2–4. To improve the reliability of the K's, the calculation has been carried out at four different wavelengths. As a reliability test of the calculations, the sum of the squared deviations (χ^2) between the experimental and calculated absorbances is reported. The stability constants K (dm^3 mol^{-1}; 25°C) and the thermodynamic parameters for **1–8** are collected in Table 5.

The comparison of the two series of compounds (**1**, **3**, **5**, **7** and **2**, **4**, **6**, **8**) shows that the K ratios between 4-oxo and 4-thioxo isologues are all greater than one, thus confirming that the electron-withdrawing effect of the C(4)=S group is higher than that of the C(4)=O [9–16].

In contrast to the inductive effect of the methyl group, compounds **3–6** show a moderate decrease in K values with respect to unsubstituted derivatives. The substitution of both the NH hydrogens (compounds **1** and **2**) produces a drastic decrease in the K values. In order to explain these results, an interaction NH $\cdots$ I, for compounds **3–8**, can be hypothesized, and this interaction should play an important role in determining the stability of the adduct. It is of interest that this hypothesis is in agreement with the results obtained in the solid state for the solved crystal structure of **3** · I$_2$ [17], **7** · I$_2$ [18], **8** · I$_2$ [18], and **8** · χ_2 I$_2$ [18] (Table 6).

In all the structures, the diiodine molecule is in the ligand plane, with the iodine bonded to the sulfur atom interacting with the NH hydrogen. In the solid **7** · I$_2$ and **8** · I$_2$ compounds, the hydrogen bond interaction involves only the N(1)H group; whereas, in solution, both NH's are engaged in the hydrogen bond formation as proven by the lowering of their vibration frequencies (Table 7).

The difference Δv (NH) can be assumed to result from an entity related to the strength of the NH $\cdots$ I interaction in the adduct; hence, a high Δv value means a strong NH $\cdots$ I interaction. This hy-

drogen bond will contribute to a stabilization of the adduct and therefore to an increase in the formation constant value; in fact, the Δv (NH) values roughly follow the increase of the K's. This seems to be confirmed by the shift of 70 cm^{-1} found for N-ethyl-imidazolidine-2-thione · I$_2$ [1] which shows a very high stability constant (>80,000 dm^3 mol^{-1} at 25°C; CH$_2$Cl$_2$). In the monomethylated compounds **3–6**, the Δv (NH) values related to N(1)H are higher than those related to N(3)H; this seems in accordance with the crystal structures of **7** · I$_2$ and **8** · I$_2$, where the iodine atom binds only the N(1)H hydrogen.

The ^{13}C NMR chemical shifts for compounds **1–8** together with those of their 1:1 adducts are reported in Table 8. The assignments for the free molecules have been made by analogy with other compounds already studied [10,19]; the two NMe methyls of compounds **1** and **2** have been assigned by comparing the chemical shift values with those of the monomethylated compounds **3**, **5** and **4**, **6**, respectively. The ^{13}C NMR chemical shifts of the adducts have been calculated as described in the Experimental section.

In all the adducts, C(2) and C(4) undergo shielding, while C(5) undergoes deshielding. Scarcely significant shifts and not always in the same direction are found for the methyls bonded to C(5). More significant shifts are found for the N-methyl groups. In consequence of adduct formation, the higher shifts of the N(1) methyls denote that the conjugation of the N(1) lone pair increases more than that of the N(3) lone pair.

As found for compounds **6** and **8** [15], also in compounds **2** and **4**, diiodine always binds the C(2)=S sulfur and, at least under the experimental condition used, the thionic C(4)=S sulfur is not involved in the coordination.

ACKNOWLEDGMENTS

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