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INTERACTION OF 3,4-DIPHENYL-1,2,5-THIADIAZOLE 1,1-DIOXIDE WITH PROTON DONOR SOLVENTS

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The UV spectra of 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide (I) and that of its thiadiazoline and thiadiazolidine derivatives were measured in several aprotic and protic solvents. Strong specific interactions of I with protic solvents are observed and the formation of stable carbinolamine type derivatives of I with methanol or ethanol is proposed. Spectroscopic data (UV, ^{1}H and ^{13}C NMR) and electrochemical evidence for their formation are given and a new thiadiazoline derivative of I (3-ethoxy-2-methyl-3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide) was synthesized. The equilibrium constant for the reaction of I with ethanol is reported.

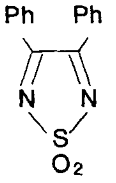
INTRODUCTION

In the context of the considerable general interest in the chemistry of 1,2,5-thiadiazole derivatives, owing to their pharmacological applications, the 1,1-dioxide derivatives are remarkable molecules of which 'only an heterogeneous series of generally unrelated reactions are know.'[1]

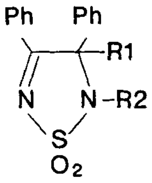
We have recently studied the voltammetric electroreduction of 3,4-diphenyl-1,2,5-thiadiazole 1,1-dioxide (**I**) in acetonitrile (ACN), including the effects of added acids,[2] and the kinetics of the hydrolysis of **I** in aqueous solution over a wide pH range.[3]

In the course of both studies, UV spectra of **I** in ethanol and ACN solutions were measured and found to be very different. This fact, together with the conclusion that **I** possesses basic properties,[2,3] suggested specific interactions of **I** with the solvents and prompted us to study them.

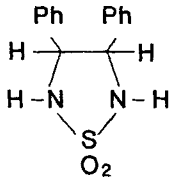
In the course of this work, some selected chemical, spectroscopic and electrochemical properties of **I** and related compounds were studied and compared. The related compounds used were 3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide (**IIa**) and 3,4-diphenyl-1,2,5-thiadiazolidine 1,1-dioxide (**III**), and also the new compound 3-ethoxy-2-methyl-3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide (**IIc**). Its synthesis is also reported as part of this work.



I



R1:R2:H IIa
R1:OCH_2CH_3 ;R2: H IIb
R1:OCH_2CH_3 ;R2: CH_3 IIc



III

In the case of solutions of **I** in ethanol, a stable but nonisolable thiadiazoline appears to form, namely 3-ethoxy-3,4-diphenyl-1,2,5-thiadiazoline 1,1-dioxide (**IIb**). Chemical, spectroscopic (UV, ^{1}H and ^{13}C NMR) and electrochemical evidence for its structure is presented.

EXPERIMENTAL

Compounds **I**, **IIa** and **III** were synthesized according to reported methods.[4] The procedure for the synthesis of **IIc** is given below.

All compounds were purified by recrystallization to constant melting point. Their purity was checked by thin-layer chromatography.

Reagent-grade ACN, absolute ethanol and other solvents used were purified by standard methods.[5,6]

UV spectral measurements were made with a Zeiss-PMQ3 spectrophotometer equipped with a thermostated cell holder. Teflon-stoppered quartz cells of 1 cm optical path length were used.

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The standard electrochemical equipment for cyclic voltammetry has been described.[2] ^1H and ^{13}C NMR spectra were measured with a Bruker 200 MHz instrument.

Synthesis of IIc. Sodium (1·7 mmol) was added to $3{\cdot}33 \times 10^{-2}$ mol of absolute ethanol contained in a stoppered vessel in a dry glove-box at room temperature. After all the Na had reacted, 1 mmol of solid **I** was added; it dissolved immediately to form a light-yellow solution to which 3·6 mmol of methyl iodide were added. The reaction vessel was left overnight with magnetic stirring. A white solid separated on cooling the solution in a refrigerator. Another portion of solid product was recovered by adding water (1·5 ml) to the reaction solution. The product was filtered, recrystallized twice from ethanol and dried at 40 °C in a vacuum oven, m.p. 110·5–111·0 °C, yield 73%. ^1H and ^{13}C NMR evidence for its structure is presented later.

The purified ACN and ethanol for equilibrium measurements were kept in a dry glove-box and solutions of **I** in ethanol–ACN mixtures were prepared by adding the required amount of a stock solution of **I** in ACN to the previously thermostated solvent mixture. No clouding or precipitation was observed when following this procedure.

The absorbance of the thermostated solution was measured as a function of time at several wavelengths until a stable spectrum was obtained. The equilibration times depend on temperature and ethanol concentration, but are relatively slow, requiring, for example, as long as 3 days at 25 °C with 2 vol.-% ethanol or 20 min at 59·6 °C with 98 vol.-% ethanol.

RESULTS AND DISCUSSION

UV spectra of I and related compounds

The spectral parameters λ_{max} and ε_{max} of **I**, **IIa**, **III** and **IIc**, measured in several solvents, are given in Table 1. The spectra of **I** in polar aprotic solvents present a relatively intense band at *ca* 325 nm ($\varepsilon \approx 10^4$ l mol^{-1} cm^{-1}). Its λ_{max} shifts with the solvent. Although this shift is poorly correlated with the inverse of solvent dielectric constant, it increases smoothly with the acceptor number[7] of the polar aprotic solvents, suggesting specific interactions of **I** with the solvents.

An interesting phenomenon is observed when proton-donor solvents are used, since a large shift to lower wavelength occurs, causing λ_{max} of **I** in alcohols and

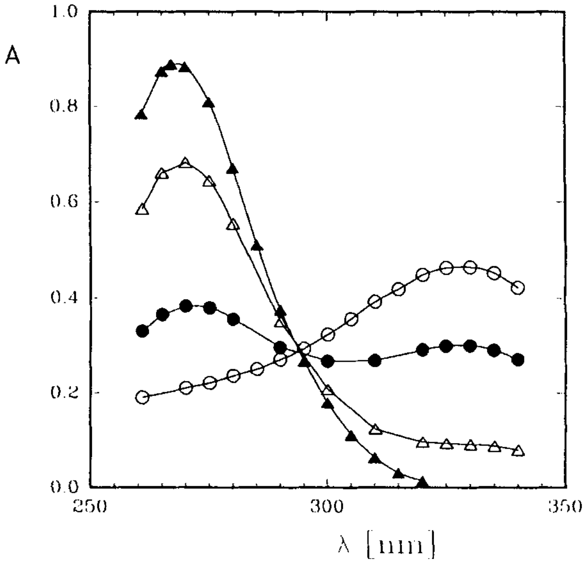

Figure 1. UV spectra of **I** in ethanol–ACN at different times and in the pure solvents. $[\mathbf{I}] = 5{\cdot}2 \times 10^{-5}$ M for all spectra and $[EtOH] = 1{\cdot}67$ M and $[ACN] = 17{\cdot}2$ M for the time-dependent spectra. (○) $t = 0$ (the spectrum is coincident with that of **I** in pure ACN); (●) $t = 1020$ min; (△) $t = 7200$ min; (▲) spectrum of **I** in pure ethanol

Table 1. UV spectroscopic parameters of **I**, **IIa**, **III** and **IIc** in different solvents at 25 °C

	I		**IIa**		**III**		**IIc**	
Solvent	λ_{max} (nm)	ε_{max} (l mol^{-1} cm^{-1})	λ_{max} (nm)	ε_{max} (l mol^{-1} cm^{-1})	λ_{max} (nm)	ε_{max} (l mol^{-1} cm^{-1})	λ_{max} (nm)	ε_{max} (l mol^{-1} cm^{-1})
Cyclohexane	317	—						
Dioxane	322	9851						
Dimethylformamide	325	—						
Acetonitrile	328	8861	260	15874	259	351	272	17333
Chloroform	333	10038						
Ethanol	267	16417	268	16102	259	360	272	13980
Methanol	267	15500	262	12367				
Water	269	15632						

water to be placed in the same spectral region of **IIa**, **III** and **IIc** absorptions, which do not exhibit this shift.

When a stock solution of **I** in ACN is added to a mixed ethanol–ACN solvent, the UV spectrum changes with time. A gradual decrease in the 328 nm band and a corresponding increase in the 267 nm band take place (Fig. 1) around an isosbestic point at *ca* 290 nm. The rate of change increases with increasing ethanol concentration and an equilibrium spectrum is obtained in all cases. The same isosbestic point is observed in the equilibrium spectra obtained with different ethanol to ACN molar ratios, and the equilibrium relative intensity of the 267 vs the 328 nm band increases with increasing ethanol content. These equilibrated spectra are temperature dependent, as the 328 nm band is favoured by an increase in temperature.

Further, when solutions of **I** in ACN are evaporated at ambient temperature and reduced pressure and the residual solid is dissolved in ethanol, evaporated by the same procedure and the residue dissolved in ACN, the initial and final spectra in ACN are identical. The spectrum in ethanol is also identical with that of a sample of **I** directly dissolved in ethanol.

We have already reported that the UV spectrum of **I** in aqueous solution is independent of the pH of the solution.[3] This was also found to hold for the solvents ACN and ethanol.

Interpretation of UV spectroscopic observations

Since the heterocyclic ring in these 1,1-dioxide derivatives behaves similarly to a strong acyl function for C-3 and C-4 substituents[1] and the reported spectral data for related compounds indicate that the heterocycle shows only a terminal absorption beyond 220 nm,[8] it must be concluded that the observed UV peaks are mainly caused by the acyl-like substituted phenyl rings.

Thus, on going from **III** to **IIa** and **I** in, for example, ACN, the shift to higher wavelength and the increase in intensity should correspond to increasingly efficient transmission of the sulfonyl group inductive effect and perhaps to some conjugation, although this is considered to be slight owing to strong steric hindrance to coplanarity.[9]

The change in the spectrum of **I** when proton-donor solvents are used, the isosbestic point observed in ethanol–ACN solvent mixtures and the temperature dependence of the spectrum indicate a reaction with the solvent. The resulting product should bear some similarity to a thiadiazoline, as suggested by their spectra.

Clearly, the formation of the postulated compound, **IIb**, explains the observed facts.

The baffling independence of the spectrum of **I** of pH, especially considering that protonated species are postulated in both aqueous solution kinetic[3] and ACN solution electrochemical[2] experiments, is also explained by the above model: since the spectrum of **I** is determined by the acyl-like substituted phenyl rings, protonation (in ACN) at the N lone pair should not change the spectrum drastically. In proton-donor solvents a very important spectral change is brought about, even without protonation, by the formation of the thiadiazoline adduct, which modifies the heterocycle.

Nuclear magnetic resonance results

The ^{1}H NMR spectrum of **IIc** in ACN-d_3 presents a complex signal (10 H), corresponding to the phenyl rings at *ca* 8 ppm (TMS), an ABX_3 system at 3·4 and 3·8 ppm (1 H each), corresponding to the non-equivalent methylenic protons, an *N*-CH_3 peak (3 H) at 2·6 ppm and a triplet (3 H) at 1·6 ppm which is assigned to the CH_3—C—O equally coupled to each methylenic proton.

The ^{13}C NMR spectrum of **IIc** has two methyl carbon signals at 14·5 and 24·4 ppm, a methylene carbon signal at 60·6 ppm and seven aromatic carbon signals between 126 and 136 ppm. The heterocyclic ring carbons are observed at 99 ppm (sp^3 C-3) and 177 ppm (sp^2 C-4). Both NMR spectra confirm the proposed structure.

The ^{13}C NMR spectrum of a solution of **I** in THF-d_8 presents four signals between 130 and 135 ppm, corresponding to the equivalent phenyl rings, and one signal at 168 ppm, corresponding to the equivalent sp^2 C-3 and C-4 heterocyclic carbon atoms; however, when methanol-d_4 is added to the solution, the ^{13}C NMR spectrum changes slowly. The phenyl resonance region becomes more complex and similar in appearance to the corresponding signals in the spectrum of **IIc** and the signal at 168 ppm (C-3, C-4) disappears and is replaced by resonances at 100·5 (C-3) and 176·7 ppm (C-4). These are the expected results for the postulated formation of a thiadiazoline adduct; the methoxy substituent itself could not be observed as it is obscured by the methanol solvent resonance.

Electrochemical results

The cyclic voltammetric electroreduction signal of **I** in ACN, which is observed at −0·8 V vs Ag^+/Ag,[2] decreases with time after addition of ethanol while an electroreduction peak at *ca* −1·8 V increases simultaneously. Since **IIa**[2] and **IIc** are reduced voltammetrically at −1·75 V, the observed change parallels the spectral observations and is in agreement with the formation of a thiadiazoline-type adduct. Further work on the electrochemical properties of **I**, **IIa** and **IIc** in ACN and mixed ACN–EtOH solvents is in progress.

Spectrophotometric evaluation of *K*

Solutions of **I**, ranging in initial concentration (I_0) from

$1\cdot97$ to $11\cdot6\times10^{-5}$ M, in mixed ethanol–ACN solvents in which the ethanol content ($\mathrm{Et_O}$) was varied from 0·328 to 11·16 M, were measured spectrophotometrically at 267, 280, 300 and 328 nm until constant absorbance values were obtained. The measurements were made at 25·0, 49·0 and 59·6 °C.

Since $K = [\mathbf{IIb}]/[\mathbf{I}][\mathrm{EtOH}]$, $[\mathbf{I}] = I_0 - [\mathbf{IIb}]$, $A^{\lambda} = \varepsilon^{\lambda}_{\mathrm{IIb}}[\mathbf{IIb}] + \varepsilon^{\lambda}_{\mathrm{I}}[\mathbf{I}]$ and $A^{328} = \varepsilon_{\mathrm{I}}^{328}[\mathbf{I}]$, a Benesi–Hildebrand-type equation can be readily obtained:

$$[\mathrm{EtOH}] \times I_0/A^{\lambda}_{\mathrm{c}} = 1/(K\varepsilon^{\lambda}_{\mathrm{IIb}}) + [\mathrm{EtOH}]/\varepsilon^{\lambda}_{\mathrm{IIb}} \qquad (1)$$

where $A^{\lambda}_{\mathrm{c}} = A^{\lambda} - \varepsilon^{\lambda}_{\mathrm{I}}\,[\mathbf{I}]$ is the absorbance of **IIb** at the chosen wavelength. The equilibrium concentration of **I** in the expression for A^{λ}_{c} is replaced by the equivalent spectral measurement: $A^{328}/\varepsilon_{\mathrm{I}}^{328}$ ($\varepsilon_{\mathrm{I}}^{328} = 8861\ \mathrm{l\,mol^{-1}\,cm^{-1}}$).

The experimental measurements used for the calculation of K and $\varepsilon_{\mathrm{IIb}}$ at $\lambda = 267$ nm are given in Table 2. The linear behaviour of equation (1) (correlation coefficient $r > 0\cdot998$) is observed at all temperatures and wavelengths used. It should also be noted that, since $[\mathrm{EtOH}]K = [\mathbf{IIb}]/[\mathbf{I}]$, the ethanol concentrations used imply suitable concentration ratios of the molecular species of **I** for the measurement of K.[10]

Mean values of the calculated equilibrium constant are given in Table 3, along with the calculated molar absorptivities for all experimental temperatures and wavelengths. These are compared with the experimentally measured $\varepsilon_{\mathrm{IIb}}$ in ethanol solutions of **I**.

Table 2. Spectroscopic measurements of **I** in ACN–ethanol for K and $\varepsilon^{267}_{\mathrm{IIb}}$ determination

Temperature (°C)	[EtOH] (M)	[I] (M × 10^5)	Equilibrium absorbance at 267 nm	Equilibrium absorbance at 328 nm
25·0	0·328	1·969	0·179	0·087
	0·529	10·167	1·227	0·277
	0·848	10·904	1·525	0·337
	1·355	10·697	1·597	0·223
	1·503	5·959	0·927	0·117
	1·716	10·167	1·523	0·164
	2·789	11·619	1·870	0·150
	3·346	11·619	1·593	0·082
	3·413	10·167	1·850	0·163
49·0	0·529	10·167	0·898	0·514
	0·848	10·904	1·203	0·612
	1·716	10·167	1·222	0·346
	3·413	10·167	1·392	0·201
	6·603	10·450	1·613	0·132
	11·155	11·475	1·733	0·074
59·6	0·529	10·167	0·802	0·587
	0·848	10·904	1·082	0·804
	1·716	10·167	1·063	0·429
	3·413	10·167	1·273	0·264

Table 3. Calculated [equation (1)] values of K and **IIb** molar absorptivities (ε)[a]

Temperature (°C)	$\varepsilon^{\lambda}_{\mathrm{IIb}} \times 10^{-3}$ at 267 nm	280 nm	300 nm	K (l mol^{-1})
25·0	16·8 ± 0·3	13·2 ± 0·3	3·7 ± 0·2	3·3 ± 0·2
49·0	15·1 ± 0·3	13·0 ± 0·4	3·6 ± 0·2	0·9 ± 0·2
59·6	14 ± 1	11·7 ± 0·8	3·3 ± 0·3	0·6 ± 0·1
ε(mean)	15·3	12·6	3·5	
ε(meas.)	16·4 ± 0·8	13·0 ± 0·6	3·5 ± 0·2	

[a] Reported uncertainties are σ from least-squares adjustments; ε(meas.) are the experimentally measured values for **I** in ethanol solution at 25 °C, and their reported uncertainties are deviations from the means of five determinations.

The agreement is reasonable and it can be also observed that the calculated $\varepsilon_{\mathrm{IIb}}$ values do not depend (within the experimental error) on temperature. This supports the 1 : 1 stoichiometry for the reaction.

The dependence of ln K on the inverse of absolute temperature ($r = 0{\cdot}999$) allows the estimation of $\Delta H^{\circ} = -41$ kJ mol^{-1} and $\Delta S^{\circ} = -127$ J K^{-1}mol^{-1}.

Kinetic measurements

In following the time evolution of the absorbance at 267 and 328 nm (i.e. $\lambda_{\max}$ for **I** in ethanol and ACN, respectively) to determine the attainment of equilibrium, kinetic measurements were made for **I** solutions in ethanol–ACN solvent mixtures of molar concentration ratio $R = [\mathrm{EtOH}]/[\mathrm{ACN}]$ ranging from 0·02 to 40 and at 25·0, 49·0 and 59·6 °C.

Linear plots of $\ln(A_t^{\lambda} - A_{\infty}^{\lambda})$ as a function of time were obtained and the observed pseudo-first-order rate constant (k_{obs}) was independent of wavelength and of **I** concentration in the experimental range used (2×10^{-5}–12×10^{-5} M).

For the simple equilibrium reaction mechanism,

$$\mathbf{I} + \mathrm{EtOH} \underset{k_b}{\overset{k_f}{\rightleftharpoons}} \mathbf{IIb}$$

$k_{\mathrm{obs}} = k_f[\mathrm{EtOH}] + k_b$. However, the experimental dependence of k_{obs} is more complex, as exemplified in Table 4 for the data at 25·0 °C, where it can be seen that k_{obs} remains almost constant up to $[\mathrm{EtOH}] \approx 1{\cdot}5$ M, increasing linearly (regression coefficient = 0·998) for higher ethanol concentrations.

Of course, an unknown part of the change in k_{obs} on going from almost pure ACN to almost pure ethanol solvent must be due to medium effects. Nevertheless, these are expected to be small, since the dielectric constants and empirical polar properties of ACN and ethanol are not very different and the reaction involves neutral bipolar molecules.

Table 4. k_{obs} at 25·0 °C for different concentrations of **I** and ethanol

[**I**] (M × 10^5)	[EtOH] M	k_{obs} (h^{-1})
1·619	0·328	0·043
4·904	0·328	0·046
12·67	0·328	0·041
10·17	0·529	0·026
6·33	0·539	0·026
10·90	0·857	0·048
6·13	1·045	0·034
10·70	1·355	0·042
5·96	1·503	0·036
10·17	1·716	0·172
5·70	2·185	0·099
11·62	2·789	0·155
11·62	3·346	0·167
10·17	3·416	—
11·40	7·219	1·14
11·40	11·76	2·18
6·54	15·369	3·23
11·43	16·730	3·37

This was confirmed in an experiment performed at 25 °C with $R = 7{\cdot}47$ ($[\mathrm{EtOH}] = 10{\cdot}23$; $[\mathrm{ACN}] = 1{\cdot}37$ M) in a medium in which cyclohexane had been added up to 3·03 M concentration. Under these conditions $k_{\mathrm{obs}} = 1{\cdot}37\ \mathrm{h}^{-1}$. A very similar value ($k_{\mathrm{obs}} = 1{\cdot}80\ \mathrm{h}^{-1}$) was measured for the same ethanol concentrations but without added cyclohexane.

A qualitative mechanistic interpretation of the dependence of k_{obs} on ethanol concentration (neglecting the unknown effect of medium change) can be given if it is considered that **I** interacts with polar solvents, as indicated by the spectral measurements and also as suggested by the basic properties of **I**.

It therefore seems reasonable to assume that **I** interacts strongly with polar ACN molecules and the replacement of ACN by ethanol at the reactive centre of **I** to form a molecular complex might be a necessary previous step. This can be represented as

$$\mathbf{I}{\cdot}(\mathrm{ACN})_n + \mathrm{EtOH} \rightleftharpoons \mathbf{I}{\cdot}(\mathrm{ACN})_{n-x}{\cdot}\mathrm{EtOH} + x\mathrm{ACN}$$

The $\mathbf{I}{\cdot}(\mathrm{ACN})_{n-x}{\cdot}\mathrm{EtOH}$ molecular complex will probably not be distinguished from **I** in our spectral measurements. Its build-up will depend on the statistical availability of EtOH to replace exchanging ACN molecules of $\mathbf{I}{\cdot}(\mathrm{ACN})_n$. At higher ethanol concentration the rate of formation of the ethanol molecular complex will increase and its rearrangement to form **IIb** will become the rate-determining step.

CONCLUSIONS

The equilibrium reported here represents the formation of a species which is usually postulated as an intermediate in condensation and hydrolysis reactions involving carbon–nitrogen double bonds. The same type of equilibrium should be operative in other protic solvents, such as water (in which **I** hydrolyses to sulfamide and benzil), where the reactive species must therefore be identified with the carbinolamine itself rather than with **I**,[3] and in the mixed water–ethanol solvent system, in which the hydrolysis reaction of **I** is currently being studied.

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