Tautomerism and Dimerization of Acetamidothiazole Derivatives − UV/Vis and NMR Spectroscopic Investigation

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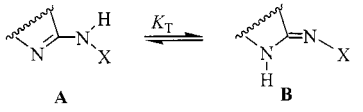
Amido (**A**)/imido (**B**) tautomerism has been investigated by UV/Vis and NMR spectroscopic methods for a number of 2-acetamidothiazoles and 2-acetamidobenzothiazoles, without the use of the physical properties of "fixed parents". The addition of polar substances to solutions of selected compounds in apolar solvents (carbon tetrachloride, dichloromethane) strongly affects the [**B**]/[**A**] ratios. Data show that the shift of the tautomeric equilibrium **A**/**B** towards the **B** form has two main causes: (i) increase of the polarity of the medium, and (ii) a base effect on the stabilization of the **B** form. The experimental ΔH and ΔS values indicate (in agreement with ^{1}H NMR spectroscopic data) that the self-assembly of 2-acetamido derivatives is a very important factor in determining the position of the tautomeric equilibrium.

Introduction

Tautomerism of heterocycles is a subject of extensive investigation from different points of view.[1,2] Our interest focuses on 1,3-thiazole and benzothiazole systems with potential amino, hydroxy, mercapto, and alkyl groups bound at position 2 of the thiazole ring, with particular attention devoted to 2-aminothiazole and its derivatives.[3−11] We have recently[12,13] proposed a simple method for evaluating the positions of tautomeric equilibria of 2-aminoazoles bearing electron-withdrawing substituents on the exocyclic nitrogen atom (see Scheme 1), by using UV/Vis spectrophotometric data.



A **B**

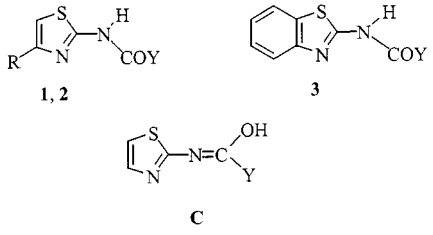
X = 2, 4, 6-trinitrophenyl,[6,8] 2,4-dinitrophenyl,[6,8] substituted acetyl groups[7]

Scheme 1. Tautomerism of 2-aminoazoles

The proposed method avoids the use of physical properties of "fixed parents"[1,14,15] (usually methyl derivatives of the two forms **A** and **B** in Scheme 1). The starting point required for the method is the observation that **A** (or **B**) is the most populated tautomer in a particular solvent. The tautomeric equilibrium can be shifted towards the other tautomer by the simple addition of substances that change the immediate neighborhood of the solute.

In principle, two main classes of parameters are responsible for the predominance of one tautomer over others: (i) external parameters: hydrogen bond interactions, polarity of the medium, acidity; (ii) internal parameters: energy of isolated molecule, molecular geometry, intramolecular hydrogen bonding interactions, electronic distribution, presence of electron-withdrawing groups.

To learn more about the mechanism of the tautomeric process in Scheme 1, we report some data on the effect of added substances on the position of the Scheme 1 type equilibrium of 2-acetamidothiazoles and 2-acetamidobenzothiazoles (Scheme 2) ascertained by UV/Vis spectroscopic methods, by ^{1}H NMR measurements of selected compounds, and by the effect of changes in temperature on the [**B**]/[**A**] ratios.

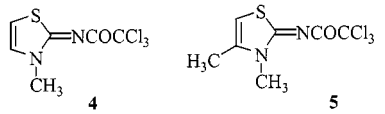


1, 2 **3**

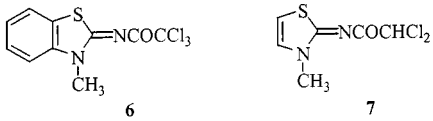
C

R = H (**1**), CH_3 (**2**);
Y = **a**) CH_3, **b**) $CHCl_2$, **c**) CCl_3, **d**) CF_3.

Scheme 2



4 **5**



6 **7**

Scheme 3

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Results

When Y is a strongly electron-withdrawing group we have no evidence of the presence of other tautomeric forms such as **C** (Scheme 2), although their presence cannot be ruled out completely. Additionally, tautomer **C** may be considered improbable in these systems since the spectroscopic properties of reported tautomers are very close to those of the fixed parents.[10,11,13]

UV/Vis Spectrophotometric Measurements

Table 1 gives slopes of plots of [**B**]/[**A**] ratios (of **1c**, **2c**, **2d**, **3c**, and **3d**, in CCl_4 or in CH_2Cl_2) versus the concentration of added polar substances (dimethyl sulfoxide, methanol, dimethylformamide, tetrahydrofuran, triethylamine) together with some statistical and spectroscopic data. In the concentration ranges reported here, these plots are linear and [**B**]/[**A**] ratios are independent of the stoichiometric concentrations of potential tautomers (see Table 7 in the Exp. Sect.). The spectrum obtained without polar substance addition is close to the spectrum of the fixed amino form,[10] while the spectrum in the presence of excess of polar substances is similar to that of the fixed imino form (**4**, **5**, **6**).

With less electron-withdrawing groups (such as Y = $CHCl_2$ in **1b**) some evidence for the presence of form **B** is obtained on addition (in DMSO) of a highly polar substance such as formamide. The spectrum of **1b** (λ_{max} 287.1 nm $\varepsilon = 1.2\cdot10^4$) becomes very similar to that of **7** (λ_{max} 310.6 nm $\varepsilon = 1.3\cdot10^4$) after addition of formamide; Figure 1 reports the effect of added formamide on the λ_{max} value of **1b** (in DMSO). Unfortunately, all attempts to determine the [**B**]/[**A**] ratio of **2b** had low levels of reproducibility.

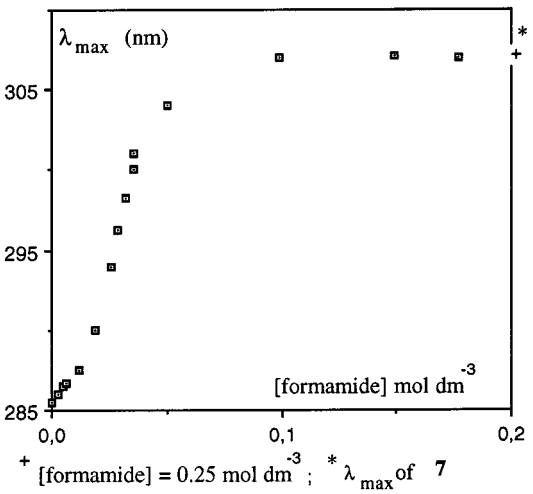


Figure 1. Plot of λ_{max} values of **1b** in CCl_4, versus formamide values

It is of interest to observe that the reverse process (from **B** to **A**) can also be observed. When **1b** (which is in the **A** form in CCl_4 or in DMSO) is dissolved in DMFA and CCl_4 is added, the λ_{max} value shifts from 303.6 nm (form **B**) to 285.0 nm (form **A**) at $[CCl_4] = 5-6$ mol dm^{-3}. Obviously, **B** is shifted towards **A** only after addition of very large amounts of CCl_4 to DMFA solutions of **1b**. The plot of λ_{max} versus $[CCl_4]$ values roughly represents the inverse of the plot in Figure 1.

UV/Vis spectrophotometric measurements at different temperatures (from 18 to 40 °C) were performed. Table 2 summarizes ΔH and ΔS values calculated for a number of **A/B** equilibria. Both ΔH and ΔS values are weakly affected, for both aprotic (DMSO, DMFA) and protic (MeOH) solutes, by the change in the amount of polar solute.

Table 1. Slopes (S) of plots of ratios [**B**]/[**A**] vs. concentration values of added substances in CCl_4 (unless otherwise indicated) at 25 °C

[Compound[a] × 10^5]	[Added substance][b]	S[c]	n[d]	R[e]	λ_{max}[f]	ε[f]
3c (5.2)	MeOH (from $3\cdot10^{-2}$ to $4\cdot10^{-1}$)	5.54±0.2	8	0.995	307	13200
3c (5.9)	DMFA (from 10^{-3} to $5\cdot10^{-2}$)	79.1±0.1	9	0.999	319	19900
3c (5.9)	THF (from $3\cdot10^{-2}$ to $7\cdot10^{-1}$)	3.27±0.1	8	0.992	317	13200
3c (4.8)	TEA (from $2\cdot10^{-3}$ to 10^{-2})	132±7	7	0.993	330	14300
3c	DMSO	451[g]	–	–	–	–
3d	DMSO	1.320[g]	–	–	–	–
2d	DMSO	321[g]	–	–	–	–
2c (9.4)	MeOH (from $2\cdot10^{-1}$ to 2)	0.524±0.01	6	0.999	314	5200
2c	DMSO	224[g]	–	–	–	–
1c (13.1)[h]	DMSO (from 10^{-2} to 10^{-1})	17.3±0.7	10	0.993	307	7200
1c (11.5)[h]	TEA (from $3\cdot10^{-2}$ to $4\cdot10^{-1}$)	2630±200	6	0.991	310	8900
1c (540)[i]	TEA (from $3\cdot10^{-3}$ to 10^{-2})	373±22[j]	10	0.986	–	–
1c (500)[i]	TEA (from $7\cdot10^{-4}$ to $7\cdot10^{-3}$)	333±14[j]	10	0.993	–	–
1c (500)[i]	TEA (from $3\cdot10^{-3}$ to $7\cdot10^{-3}$)	391±19[k]	7	0.994	–	–
1c (540)[i]	TEA (from $7\cdot10^{-4}$ to $5\cdot10^{-3}$)	441±26[k]	6	0.993	–	–

[a] In mol·dm^{-3}. – [b] Range of concentration in mol·dm^{-3}. – [c] Errors are standard deviations. – [d] Number of points. – [e] Coefficient of correlation. – [f] Assigned to form **B**. – [g] Ref.[7] – [h] In CH_2Cl_2. – [i] In $CDCl_3$ at 20 °C. – [j] [**B**]/[**A**] values calculated from δ_{H5} values. – [k] [**B**]/[**A**] values calculated from δ_{H4} values.

Table 2. ΔH and ΔS values for the **A**/**B** equilibrium in CCl_4 (unless otherwise indicated) and in the presence of polar solutes; temperature range 18−40 °C

Substrate[a]	Solute	ΔH [kcal mol^{-1}]	$-\Delta S$ [cal mol^{-1}K^{-1}]
1c (9.4)[b]	DMSO	8.8±0.4	29±1
1c (9.4)[b]	TEA	12.2±0.5	40±2
2c (9.4)	DMSO	4.8±0.3	15±1
2c (9.4)	MeOH	4.3±0.3	14±1
3c (5.2)	DMSO	8.0±0.9	28±3
3c (5.2)	MeOH	5.7±0.4	18±2
3c (5.9)	DMFA	8.7±0.2	30±0.5
3c (5.9)	THF	5.1±0.2	17±0.7
3c (5.3)	TEA	9.6±1	33±4

[a] Concentration values × 10^5 mol·dm^{-3}. − [b] In dichloromethane.

NMR signals of the compounds considered here are very similar in $CDCl_3$ and in [D_6]DMSO. The observed differences are smaller for potential tautomers **1c**, **2c**, and **3c** than for the fixed parents **4**, **5**, and **6**. Clearly, there is a solvent effect acting on the ^{1}H NMR signals of the fixed compounds.

The addition of [D_6]DMSO to $CDCl_3$ solutions of **1c** and **2c** produced a shift of H signals in the opposite direction to that expected[16,17] on the basis of the ^{1}H signals of fixed tautomers. The effect of the medium is eclipsed by the shift of the tautomeric equilibrium and does not allow the [**B**]/[**A**] ratios to be determined.

Useful information can be obtained from the analysis of ^{1}H-^{1}H NOE interactions displayed by compound **1c** in [D_6]DMSO. When 4-H is irradiated, a relevant enhancement of the NH signal is detected, indicating the presence of the imido tautomer **B** in this more polar solvent. Were the amido (aromatic) form **A** the most populated tautomer, this enhancement would have not been observed, because of the greater distance between 4-H and NH protons.

Table 3. ^{1}H and ^{13}C NMR spectroscopic data of selected 2-thiazolamine derivatives

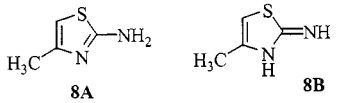
Compound	Solvent	NH	4-H	5-H	CH_3	C-2	C-4	C-5	C=O	CCl_3	CH_3
1b	$CDCl_3$	11.97	7.69 d ^3J 3.7	7.17 d ^3J 3.7	6.28[a]	159.35	135.70	114.85	162.53	65.44[a]	–
1b	[D_6]DMSO	13.04	7.56 ^3J 3.7	7.36 ^3J 3.7	6.66[a]	159.03	136.25	114.65	163.35	66.58[a]	–
1c	$CDCl_3$	10.90	7.55 d ^3J 4.7	7.14 d ^3J 4.7	–	160.02	136.25	114.99	161.22	91.89	–
1c	[D_6]DMSO	13.97	7.61 d ^3J 4.4	7.28 d ^3J 4.4	–	171.13	125.94	112.82	168.26	95.93	–
2c	$CDCl_3$	10.00	–	6.68 q ^4J 1.0	2.42 d ^4J 1.0	159.77	144.51	109.50	161.37	91.99	16.00
2c	[D_6]DMSO	13.84	–	6.83 q ^4J 1.2	2.24 d ^4J 1.2	171.32	135.10	107.18	168.37	96.09	13.34
4	$CDCl_3$	–	7.13 d ^3J 4.6	6.88 d ^3J 4.6	3.87	170.13	127.69	111.06	170.00	95.85	36.11
4	[D_6]DMSO	–	7.74 d ^3J 4.6	7.33 d ^3J 4.6	3.78	168.92	129.95	111.31	168.21	96.02	35.90
5[b]	$CDCl_3$	–	–	6.51 q ^4J 1.2	3.80	170.95	135.75	106.11	169.71	96.04	33.34
5[c]	[D_6]DMSO	–	–	7.00 q ^4J 1.0	3.74	169.52	137.34	106.22	167.96	96.14	33.27
8A	$CDCl_3$	4.70[d]	–	6.10	2.23	167.50	148.45	102.40	–	–	17.10
8A	[D_6]DMSO	6.81	–	6.08	2.05	167.96	147.60	100.35	–	–	17.30

[a] CO*CH*Cl_2. − [b] Other signals: δ_H = 2.38 d (3 H, ^4J 1.2, CH_3), δ_C = 14.32 (CH_3). − [c] Other signals: δ_H = 2.36 d (3 H, ^4J 1.0, CH_3), δ_C = 13.57 (CH_3). − [d] At [**8A**] = 2·10^{-3} mol dm^{-3}.

NMR Measurements

Table 3 reports ^{1}H and ^{13}C NMR spectroscopic data for selected potential tautomers and of some fixed parents **4**, **5**, **6**, and of 2-amino-4-methylthiazole (**8A**) (Scheme 4). Spectroscopic data for derivatives of benzothiazole are shown in Table 4.

In addition to the UV/Vis method, discrimination between tautomers in thiazolamine systems should in principle be aided by ^{1}H NMR spectroscopic data.[16,17] ^{1}H NMR signals of the compounds considered here are very similar in $CDCl_3$ and in [D_6]DMSO. The observed differences are smaller for potential tautomers **1c**, **2c**, and **3c** than for the fixed parents **4**, **5**, and **6**. Clearly, there is a solvent effect acting on the ^{1}H NMR signals of the fixed compounds.



8A **8B**

Scheme 4

More informative is the analysis of the ^{13}C chemical shifts, which show significant differences between the two solvents for **1c**, **2c**, and **3c**. In compounds **1c** and **2c**, the most relevant shift difference concerns the signals of C-2 (δ = 171 in compounds **1c** and **2c**) and C-4 (δ = 126 for **1c** and δ = 135 for **2c**), which are deshielded and shielded, respectively, by over 10 ppm in [D_6]DMSO, relative to their counterparts in $CDCl_3$ (δ_{C2} = 160 for **1c** and **2c**; δ_{C4} = 136 for **1c** and 145 for **2c**). Other important shifts are observed for the carbonyl and for the CCl_3 carbon atoms. The signals in [D_6]DMSO solutions ($\delta_{C=O}$ = 168, δ_{CCl3} = 96) are very

Table 4. ^1H and ^{13}C NMR spectroscopic data of selected 2-benzothiazolamine derivatives

Compound	Solvent	NH	4-H	7-H	5-H	6-H	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C=O	CCl_3
3c	$CDCl_3$	9.14	7.87 d	7.79 d	7.40 td	7.51 td	160.09[a]	121.88	124.95	127.02	119.87	131.09	145.18	162.19[a]	91.86
				^3J 8.0	^3J 7.7	^3J 7.7	^3J 7.7								
					^4J 1.2	^4J 1.2									
3c	$[D_6]$DMSO	14.42	7.54 m	8.01 d	7.54 m	7.41 m	171.00	114.23	127.56	124.34	123.10	126.95	136.44	169.24	95.55
				^3J 7.9											
3c	$[D_8]$THF	10.8	7.56 bd	7.86 d	7.46 td	7.33 td	169.82	116.00	127.94	125.01	123.42	129.62	139.97	168.76	96.07
			^3J 8.0	^3J 8.0	^3J 7.7	^3J 7.6									
					^4J 1.2	^4J 1.2									
6[b]	$CDCl_3$		7.47 d	7.78 d	7.56 td	7.42 td	170.84	112.14	127.65	124.91	123.11	126.46	137.22	170.74	95.65
				^3J 7.7	^3J 7.8	^3J 7.7	^3J 7.5								
					^4J 1.2	^4J 1.2									
6[c]	$[D_6]$DMSO		7.81 d	8.07 d	7.64 td	7.48 td	169.92	113.64,	127.84	125.04	123.39	125.41	137.23	169.32	95.65
			^3J 8.2	^3J 7.7	^3J 7.8	^3J 7.6									
					^4J 1.2	^4J 1.1									

[a] Tentative assignement. – [b] Other signals: δ_H = 4.00 s (3 H, CH_3); δ_C = 32.64 (CH_3). – [c] Other signals: δ_H = 3.95 s (3 H, CH_3); δ_C = 32.88 (CH_3).

close to those observed for the fixed imino tautomers **4** and **5** in the same solvent. The benzothiazole derivatives (see Table 4) also show similar behavior (compare the spectroscopic data of **3c** and **6** in $[D_6]$DMSO).

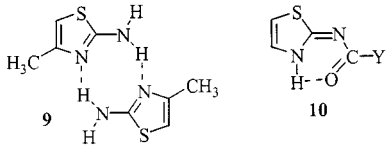
As these are the carbon atoms that undergo the main structural variations on passing from the amido **A** tautomer to the imido **B** form, ^{13}C NMR spectroscopic data confirm[12,13] that the more populated form is **A** in $CDCl_3$ and **B** in $[D_6]$DMSO. When X is $CHCl_2$, the situation changes dramatically. In this case, ^1H and ^{13}C NMR spectroscopic data (see Table 3) indicate the presence only of form **A** in both $CDCl_3$ and $[D_6]$DMSO.

^1H NMR measurements of **8A** at different concentration values in $CDCl_3$ are also of interest. When [**8A**] = $2\cdot10^{-2}$ mol dm^{-3}, the 5-H and the CH_3 signals feature double quadruplet and double doublet splittings, respectively. Addition of D_2O converts the signals into a quadruplet and a doublet, respectively. These results may indicate the presence of the imino form **8B** (Scheme 4). However, this explanation does not agree with all our previous findings or with the literature data.

When [**8A**] = $2\cdot10^{-3}$ mol dm^{-3}, the spectrum features a broad singlet arising from 5-H and a doublet for the CH_3 group. Neither irradiation of the NH signal (δ = 4.7) nor the addition of D_2O changed either signal, thus ruling out the presence of tautomer **8B** in $CDCl_3$. In $[D_6]$DMSO, the spectrum agrees with the form **8A**, which is confirmed by comparison with spectroscopic data of fixed parents.[10]

A possible explanation of this anomalous behavior lies in the formation of dimers such as **9** (Scheme 5), which can be detected at increased concentrations. In these self-associated species the presence of an H-bonded amino proton explains the increased multiplicity of the 5-H and CH_3 signals.

At [**8A**] = $2\cdot10^{-2}$ mol dm^{-3}, the spectrum does not show two different NH signals as required for **9**. Instead, only one signal – observed at δ = 5.1 (integrating for 2 protons) – is detected, at higher frequencies than those observed at



Scheme 5

lower concentrations ([**8A**] = $2\cdot10^{-3}$ mol dm^{-3}). The downfield shift with increasing concentration of **8A** suggests that the amino group progressively becomes engaged in H-bonding.

Linear dimers have been reported on the basis of IR spectroscopic data,[18] but they hardly explain the fact that all the methyl groups show coupling with NH protons. Recently, 2-aminopyridine has been observed to form open-chain-like H bonds.[19,20]

The dimeric forms of compounds reported here are probably intermediate in tautomerism. Dimer **9** is very close to the imino form **8B** both in energy and in geometry, but cannot be interpreted as **8B**. ^1H NMR spectra of compounds **1b** and **1c** in $CDCl_3$ show singlets corresponding to the NH protons, at chemical shifts between δ = 10 and 12, values typical of H-bonded protons.

A tentative structure of aggregates is based on some ^1H-^1H NOE experiments performed on compounds **1a**, **1b**, and **1c** in $CDCl_3$. The spatial interaction of the NH and 4-H protons indicates the presence of self-associated species (about 3.6 Å from an AM1 model). In fact, irradiation of the NH proton of **1a** (δ = 12.8) induces a significant enhancement of the 4-H signal. In addition, another NOE interaction involving 4-H and CH_3 protons indirectly confirm the molecular aggregation. Similar results have also been obtained for compounds **1b** and **1c**. NOE enhancements involving 5-H and NH protons have not been observed in any compound studied (**1a**, **1b**, **1c**). Dimers such as **9**, suggested here in solution, agree with those observed

by X-ray diffraction in crystals of 2-phenyliminothiazolidine[21] and of sulfathiazole.[22]

As mentioned before, **1b** does not convert into the imido tautomer in [D_6]DMSO. Despite this, the solute−solute H-bonding interaction in this solvent is less favored than that in $CDCl_3$, as indicated by an NOE effect lower in [D_6]DMSO than that observed in $CDCl_3$. The reported data disagree with the existence of an intermolecular NH···O=C hydrogen bond.

It has been postulated that acetamidothiazoles[14] exist with intramolecular H bonds as shown in **10**. However, these and previous findings[13] disagree with **10**. In particular, X-ray diffraction of **3c** indicates that the C=O group is remote from the hydrogen atom close to the ring sulfur atom.

When small amounts of triethylamine were added to solutions of **1c** in $CDCl_3$, the 4-H and 5-H signals were shifted toward lower frequencies, as required when the tautomeric equilibrium **A/B** is shifted toward the form **B**. Assuming that (i) the most populated form in $CDCl_3$ is **A**, while in the presence of an excess of TEA ($\geq 2\cdot10^{-2}$ mol dm^{-3}) **B** is the most populated form, and (ii) the forward and the back reactions are very fast, Equation (1) may be used,[23] where δ is the chemical shift of 4-H (or 5-H) of **1c** in the presence of various concentrations of TEA, δ_A is the chemical shift of 4-H (or 5-H) in $CDCl_3$ (form **A**) and δ_B refers to the chemical shifts of the same protons in the presence of an excess of TEA. P_A and P_B are the molar fraction of **A** and **B**, respectively ($P_A + P_B = 1$) and $P_B = (\delta - \delta_A)/(\delta_B - \delta_A)$.

$$\delta = P_A\delta_A + P_B\delta_B \quad (1)$$

The [**B**]/[**A**] ratios (the apparent tautomeric constant) may be calculated from P_B values and from the stoichiometric concentration of **1c**. Data are shown in Table 5. The plots of [TEA] values against [**B**]/[**A**] ratios are linear and the slopes are reported in Table 1, for two sets of independent measurements. The *S* values calculated from NMR spectroscopic data are in the same range as the *S* values obtained from UV/Vis spectrophotometric measurements.

Table 5. Effect on the[**B**]/[**A**] ratio of the addition of TEA to solutions of 2-[(trichloroacetyl)amino]thiazole (**1c**) in $CDCl_3$ at 20 °C, the apparent tautomeric constant calculated from δ_{5H} values using Equation (1)

[TEA] [10^3 mol·dm^{-3}]	[**B**]/[**A**]
2.91	0.298
3.78	0.530
4.25	0.627
4.81	0.731
6.13	1.16
7.44	1.57
8.14	1.80
9.33	2.25
9.96	2.70
10.2	2.70

Discussion

Effect of Addition of Polar Substances

Even if some differences in solvent do not permit a full comparison, the values of the slopes reported in Table 1 confirm[12,13] that the benzothiazole derivative is more sensitive to the addition of DMSO than the thiazole derivative is: $S_{3c}/S_{1c} = 27$. In this case, the DMSO effect is probably a simple effect of the polar solute on the tautomeric equilibrium. The tautomeric equilibrium is probably complicated by the simultaneous presence of different interaction mechanisms (involving H-bonding interaction as well) between the thiazole derivatives and the polar substances. In fact, E_T values or donicity number values did not give a satisfactory correlation with log*S* values.

The addition of TEA shifts the tautomeric equilibrium towards the **B** form more strongly in the thiazole than in the benzothiazole derivative. TEA is a weakly polar substance[24] and it is permissible to state that TEA acts mainly as a proton acceptor in stabilizing the **B** form. This interaction is depressed in the benzothiazole system by the condensed ring, which can exert "*peri*-like" steric hindrance on the nitrogen atom of the thiazole ring. This inversion is not observed with the less basic DMSO. The effect of the addition of TEA cannot be explained by a simple salting process, because **3c** shows DMSO to be more efficient than TEA in shifting the tautomeric equilibrium.

Clearly, the acidity of the NHCOY proton is an important factor. When Y = CH_3, no shift towards form **B** was observed. When Y = $CHCl_2$, a small UV/Vis shift was observed on adding the substances in Table 1. This was confirmed by cases in which Y = CF_3 (compounds **2d** and **3d**), in which the addition of DMSO also produced high *S* values.[13]

Methanol is moderately able to shift the equilibrium **A/B** toward **B**. The proticity of the medium is probably not an important factor and MeOH (also formamide) acts in the tautomerism pathway not as a proton donor, but in the same way as other polar substances.

Addition of polar substances in small amounts (10^{-3} to 10^{-2} mol dm^{-3}) to CCl_4 can hardly account for the substantial changes of the physical properties of the apolar solvent. A more likely explanation may be that the addition of DMSO, DMFA, MeOH, TEA, and salts[1] involves the presence of specific solute/solute interactions, which shift the tautomeric equilibrium toward the form **B**, which is more polar than **A**.

Effect of Changes in Temperature

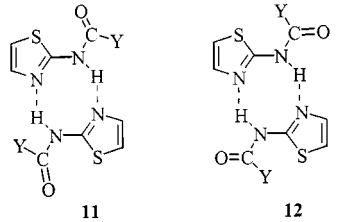
An increase in temperature produces a decrease in K_T value and a shift in the tautomeric equilibrium towards the amido aromatic form **A** (see Table 6). This behavior applies for all the substrates considered and for all the added polar solutes.

Table 6. Selected examples of the effect on [**B**]/[**A**] ratio of changes of temperature

[**2c**] = 9.4 10^{-5} mol dm^{-3}; [DMSO] = 1.8 10^{-3} mol dm^{-3}	
T [°C]	[**B**]/[**A**]
20	0.409
25	0.358
30	0.331
35	0.301
40	0.260
[**3c**] = 5.2 10^{-5} mol dm^{-3}; [MeOH] = 0.211 mol dm^{-3}	
T [°C]	[**B**]/[**A**]
20	1.42
25	1.25
30	1.07
35	0.94
40	0.813

Table 2 gives the thermodynamic parameters relating to the equilibrium **A/B**. In all the cases reported, the ΔH value is positive and ranges from 4 to 12 kcal mol^{-1}. The ΔS values are high (negative). Compound **3c** shows very similar values of ΔH and $-\Delta S$, for the addition of DMSO, DMFA, and TEA, suggesting that the action of these three substances on the tautomeric equilibrium is the same. There is probably a base stabilization of form **B**.

Poorly basic substances (THF and MeOH) show slightly lower ΔH (and $-\Delta S$) values (of **3c**) probably indicating a minor difference in interaction between **A** and **B**. Values of ΔH and $-\Delta S$ are the same for MeOH and THF (in the case of **3c**) and for MeOH and DMSO (in the case of **2c**), in agreement with the previous conclusion that no hydrogen-bond donation from the solvents is operative in the **A/B** equilibrium. The ΔS values in Table 2 (together with NOE experiments) clearly indicate a multi-step mechanism for the tautomerism in Scheme 1, involving two molecules of the thiazole derivative, such as the dimeric forms **11** and **12** (Scheme 6).

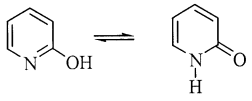


11 **12**

Scheme 6

Amides and aminoazoles are known to form dimeric aggregates. The presence of the dimeric form **11** may explain the predominance of the rotamer shown in **11**, out of all the other possible rotamers, as indicated by Katritzky and co-workers.[25] When Y = CCl_3, **11** predominates over **12** because the trichloroacetyl group may be accessed a little more easily away from the bulk sulfur atom of the thiazole ring. A weak positive interaction between the sulfur atom and the oxygen atom of the carbonyl group was suggested by X-ray diffraction data of **3c**.[13]

Compound **11** may be the intermediate of the **A/B** tautomerism. Structures such as **11** and **12** are probably sterically more hindered in benzothiazole systems than in thiazole ones. It is known that in the condensed phase the form bearing an exocyclic double bond (**B**) is more populated than form **A**, which is the most populated form in the gas phase (or in very dilute solutions). For example, the more populated form of 2-hydroxypyridine[26−28] (**13**) in the condensed phase is the oxo form, but the aromatic hydroxy form predominates in the gas phase or in very dilute solutions (Scheme 7). In the condensed phase, 2-hydroxypyridine exists mainly in a dimeric form.



13

Scheme 7. Tautomerism of 2-hydroxypyridine

A simple explanation of the effect of temperature is that its elevation may shift the equilibrium of dimer formation towards the monomers. Dimers such as **11** may be considered closer to form **B** than to form **A**, which is the more stable form of isolated thiazoleamine derivatives.

Conclusion

Previous observations performed using UV/Vis spectrophotometric methods are confirmed by the current data, which also involve ^{1}H and ^{13}C NMR measurements. In addition to the molecular structural parameters affecting the position of the tautomeric equilibrium, there are two main external parameters. These are: (i) a general effect from the medium, depending on the changes of its polarity, and (ii) a base effect stabilizing form **B**. The presence of self-association of potential tautomers is a third parameter, very important in explaining tautomeric behavior. The structure **11** for dimeric species confirms the findings reported here.

Experimental Section

General: NMR spectra (^{1}H, ^{13}C, COSY, HETCOR, and ^{1}H-^{1}H NOE) were recorded with a Varian Gemini 300 MHz instrument. The δ_H and δ_C values are expressed in ppm from the solvent peak. In NOE difference experiments, a number of transients (512) were accumulated using relaxation delays of 2−4 s, and a minimum decoupler power to obtain NOE signals. The instrumental settings were: spectral width 4.5 kHz, pulse width 12 μs (90° flip angle). ^{1}H NMR spectra were recorded at concentration values in the ranges of $1-3\cdot10^{-3}$ and $2-7\cdot10^{-2}$ mol dm^{-3}. ^{13}C NMR spectra were recorded at concentration values from $2\cdot10^{-2}$ to $5\cdot10^{-2}$ mol dm^{-3}. Discrimination between C-2 and C=O resonances was dealt with by coupled ^{13}C NMR spectra. $CDCl_3$ was dried by distillation from

P_2O_5 immediately prior to use; DMSO was dried over molecular sieves. UV/Vis spectra were recorded with Perkin−Elmer Lambda 5 and Lambda 12 spectrophotometers with a thermostatic bath (±0.05 °C).

Materials: Amide derivatives were prepared and purified by the reported procedures.[13] Solvents were commercial samples (Carlo Erba, RPE) purified by the usual procedures.[29]

Determination of [B]/[A] Ratios (by the UV/Vis Spectrophotometric Method): This was performed using the described procedures.[13] Table 7 shows an instance of [**B**]/[**A**] ratio changes on varying the concentration of DMFA in CCl_4. The solute concentration value for determining ΔH and ΔS values were appropriate for obtaining [**B**]/[**A**] ratios close to a value of 1. Some ΔH and ΔS values collected in Table 2 are means of independent determinations at different solute concentrations.

Table 7. Effect on the [**B**]/[**A**] ratio of the addition of DMFA to solution of 2-[(trichloroacetyl)amino]benzothiazole (**3c**) in CCl_4 at 25 °C

[DMFA] 10^3 (mol dm^{-3})	[**B**]/[**A**][a]
1.64	0.0993
3.29	0.296
4.93	0.386
6.58	0.565
8.22	0.795
9.86	0.801
16.4	1.38
19.4 [x]	1.53 [x]
49.3	3.92

[x] mean of several determinations at variable [**3c**] values ([DMFA]·10^3 = 19.4), such as the following:

[**3c**] 10^5 (mol dm^{-3})	[**B**]/[**A**][a]
1.47	1.61
2.93	1.59
4.40	1.50
5.87	1.39
8.80	1.57
17.6	1.54

[a] Calculated by the UV/Vis spectrophotometric method (see ref.[7]).

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