Diheteroarylmethanes. 6.[1] Probing the Electron-Withdrawing Rank of Heteroaryl Groups by Conformational Studies of Push-Pull Ethylenes. Isolation of NH-Enamine Tautomers of α,α-Diheteroarylacetaldehydes (Heteroaryl = 2-Benzoxazolyl, 2-Benzothiazolyl)

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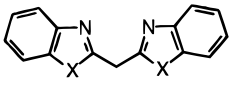
Enamines and enol ethers substituted in the β position by the 2-benzoxazolyl and 2-benzothiazolyl group have been obtained by condensing dimethylformamide dimethyl acetal and ethyl orthoformate, respectively, with bis(2-benzoxazolyl)methane and bis(2-benzothiazolyl)methane. A dynamic NMR and semiempirical (PM3) investigation on rotational energy barriers has been carried out in order to rank the electron-withdrawing capacity of the heterocyclic rings. The NMR-based evaluation of the energy barriers corresponding to the rotation along the enaminic double bond has shown that the π-electron-withdrawing power of benzothiazole is larger than that of benzoxazole, in full accord with previously obtained charge demand values based on ^{13}C and ^{15}N π-charge/shift relationships. The NMR and the computational approaches have led to consistent results. The X-ray crystal structure of α,α-bis(2-benzothiazolyl)-β-(dimethylamino)ethene shows that only one heteroaryl ring is coplanar with the enaminic double bond, while the second one is twisted by 73° relative to such a plane. Moreover, in this case calculations closely reproduce the experimental results. In the calculated transition states corresponding to the rotational process along the enamine double bond, the two heteroaryl groups become coplanar and conjugation develops between the enaminic nitrogen electron pool and both heterocycles. The lower rotational barrier observed in the case of the 2-benzothiazolyl derivatives, with respect to the 2-benzoxazolyl derivatives, is therefore a direct consequence of the higher electron-withdrawing power of the former group. Furthermore, a stabilizing intramolecular nonbonded S···S interaction in the rotational transition state of the benzothiazolyl derivatives is evidenced by the calculations. An unprecedented isolation of the NH-enamine tautomer involving the benzoxazolyl and benzothiazolyl ring in α,α-diheteroacetaldehydes has been performed, confirming these heterocycles as strong electron-withdrawing substituents.

Evidence for the "active methylene" behavior of the methylene bridge of bis(2-benzoxazolyl)methane (**1**) and bis(2-benzothiazolyl)methane (**2**) is provided by its prompt reactivity with electrophilic reagents (condensation with carbonyl compounds, *azo* coupling, nitrosation, mild oxidation).[3] The strong electron-withdrawing nature of



1: X = O

2: X = S

the pertinent heterocycles, as monitored by their high charge demands c_X^{Ph}, accounts for this type of reactivity pattern. Charge demands c_X^{Ph} of electron-withdrawing groups X are defined[4] as the fraction of πnegative charge transferred from the carbanionic carbon of benzyl carbanions $PhCH^-X$ to the group X. Charge demands allow the quantitative ranking of the π-electron-withdrawing capacity of a large variety of organic functionalities, including heterocycles.[4a−c] 2-Thiazolyl ($c_X^{Ph} = 0.395$)[2,4d] and 2-benzothiazolyl ($c_X^{Ph} = 0.464$)[2,4d] groups display larger charge demands than their oxygen counterparts, 2-oxazolyl ($c_X^{Ph} = 0.346$)[2] and 2-benzoxazolyl ($c_X^{Ph} = 0.430$).[2] An alternative measure of the π-electron-delocalizing capacity of electron-withdrawing groups is provided by the rotameric energy barriers in push-pull ethylenes.[6] Values of the energy barriers to rotation in push-pull ethylenes **3**−**6** would provide an independent measure of the electron-withdrawing capacities of the 2-benzoxazolyl and 2-benzothiazolyl groups. As "active methylene" compounds, **1** and **2** are expected[7] to react with dimethylformamide dimethyl acetal to produce the

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(1) For part 5, see ref 2. For part 4, see ref 5.

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(4) (a) Abbotto, A.; Alanzo, V.; Bradamante, S.; Pagani, G. A. *J. Chem. Soc., Perkin Trans. 2* **1991**, 481−488. (b) Abbotto, A.; Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1993**, *58*, 444−448. (c) Abbotto, A.; Bradamante, S.; Pagani, G.; Rzepa, H.; Stoppa, F. *Heterocycles* **1994**, *40*, 757−776. (d) Bradamante, S.; Pagani, G. A. *Pure Appl. Chem.* **1989**, *61*, 709−716. (e) Barchiesi, E.; Bradamante, S.; Ferraccioli, R.; Pagani, G. A. *J. Chem. Soc., Perkin Trans. 2* **1990**, 375−383. (f) Abbotto, A.; Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1993**, *58*, 449−455.

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(6) (a) Sandstrom, J. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; John Wiley and Sons: New York, 1983; Vol. 14. (b) Kleinpeter, E.; Spitzner, R.; Schroth, W. *Magn. Reson. Chem.* **1987**, *25*, 688−695. (c) Kleinpeter, E.; Spitzner, R.; Schroth, W.; Pihlaja, K. *J. Prakt. Chem.* **1990**, *332*, 841−844. (d) Kleinpeter, E.; Schroth, W. *Magn. Reson. Chem.* **1991**, *29*, 223−230. (e) Kleinpeter, E.; Thomas, S.; Uhlig, G.; Rudorf, W. D. *Magn. Reson. Chem.* **1993**, *31*, 714−721.

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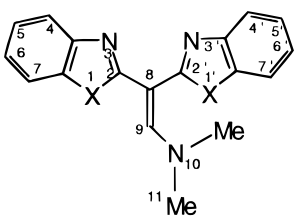
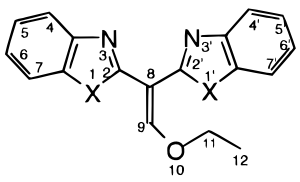
corresponding enamines **3** and **4** and with triethyl orthoformate for the vinyl ethers **5** and **6**.



3 : X = O
4 : X = S



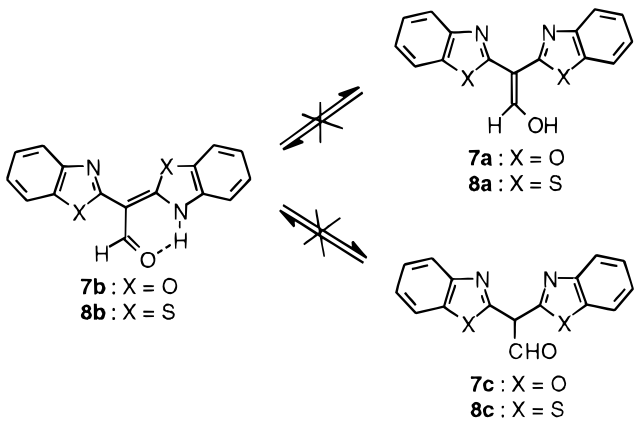
5 : X = O
6 : X = S

In this paper we describe the preparation of compounds **3**−**6** and the ^{1}H NMR-based experimental determination of the energy barriers to rotation for compounds **3** and **4**. A semiempirical evaluation of activation energies, both in the gas phase and in solution, has been carried out, and results are evaluated in light of structural parameters obtained from a diffractometric study on crystals of compound **4**. Finally, we describe that hydrolytic cleavage of enamines **3** and **4**, as well as enol ethers **5** and **6**, produces α,α-diheteroarylacetaldehydes which can be isolated and characterized in the stable form only as the enamine tautomers **7b** and **8b**. In accord with our previous findings,[2] all these results confirm that the π-electron-withdrawing capacity of benzothiazole is larger than that of benzoxazole.

Results

Synthesis. Condensation of the benzoxazole derivative **1** with dimethylformamide dimethyl acetal to give the enamine **3** requires long reaction times and high temperatures. Milder conditions are needed to perform the analogous condensation of **2**. The reaction affords two products, the most abundant one being the expected enamine **4**. The byproduct, responsible for the deep blue color that develops upon mixing the two reagents, is probably a double condensation product. Due to its very low formation yields, it was not further investigated.

Condensation of **1** and **2** with triethyl orthoformate in acetic anhydride affords the corresponding enol ethers **5** and **6**, respectively, easily cleaved hydrolytically to the corresponding enamino aldehydes **7b** and **8b**. These systems are the stable tautomers, and they are in equilibrium neither with enols **7a** and **8a** nor with formyl derivatives **7c** and **8c**.



7b : X = O
8b : X = S

7a : X = O
8a : X = S

7c : X = O
8c : X = S

(7) Abdulla, R. F.; Brinkmeyer, R. S. *Tetrahedron* **1979**, *35*, 1675−1735.

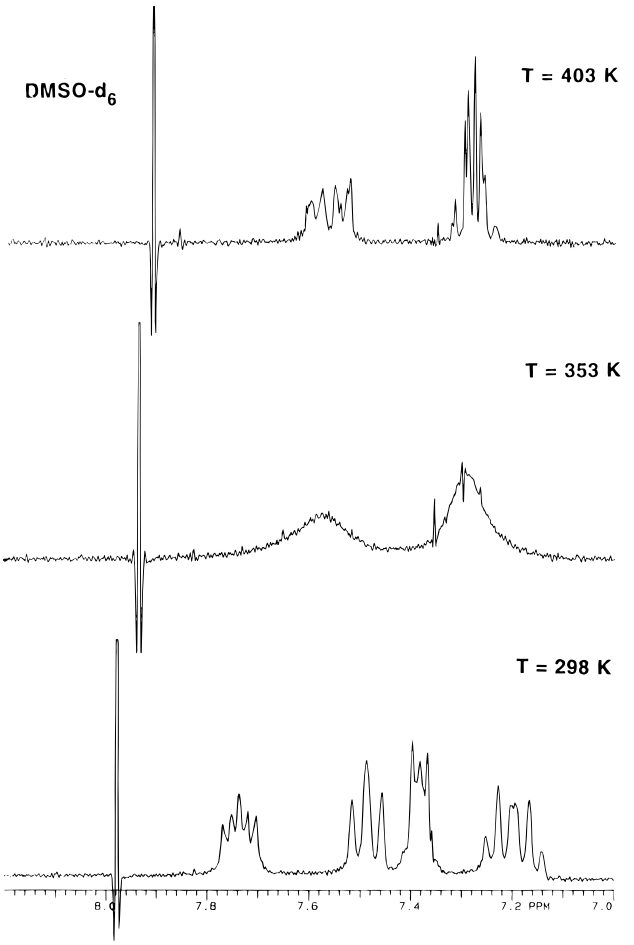


Figure 1. Variable temperature ^{1}H NMR spectra of α,α-bis-(2-benzoxazolyl)-β-(dimethylamino)ethene (**3**) (aromatic region).

NMR Group Anisochrony of Enamines 3 and 4 and Enol Ethers 5 and 6. Enamines **3** and **4** show NMR anisochronies both of the dimethylamino methyl groups and the two heteroaryl rings; both are sensitive in different ways to temperature and solvent effects. We explored the behavior of these compounds at different temperatures in different solvents prior to initiating a detailed variable temperature investigation to determine energy barriers.

^{1}H NMR spectra of enamine **3** in DMSO show that the two benzoxazolyl rings are anisochronous at room temperature and equivalent at 403 K (Figure 1) and anisochronous in $CDCl_3$ at room temperature. The two methyl groups (signals not shown in Figure 1) are responsible for two sharp singlets at 243 K ($CDCl_3$), a broad singlet at room temperature, and a singlet above 318 K.

In enamine **4** the two benzothiazolyl rings are anisochronous at room temperature in $CDCl_3$ but show a very broad pattern in DMSO. The two rings become isochronous at 353 K in DMSO. In acetone enamine **4** shows broad signals for the aromatic region at room temperature but two sharp sets of signals at 263 K (Figure 2). The two methyl groups (signals not shown in Figure 2) are responsible for two rather broad singlets at 180 K and a sharp singlet at 243 K in CS_2.

In order to perform variable temperature analysis of rotameric equilibria of enamines **3** and **4**, hygroscopic solvents such as deuterioacetone and DMSO were avoided since **3** and **4** are sensitive to hydrolysis. The best solvent

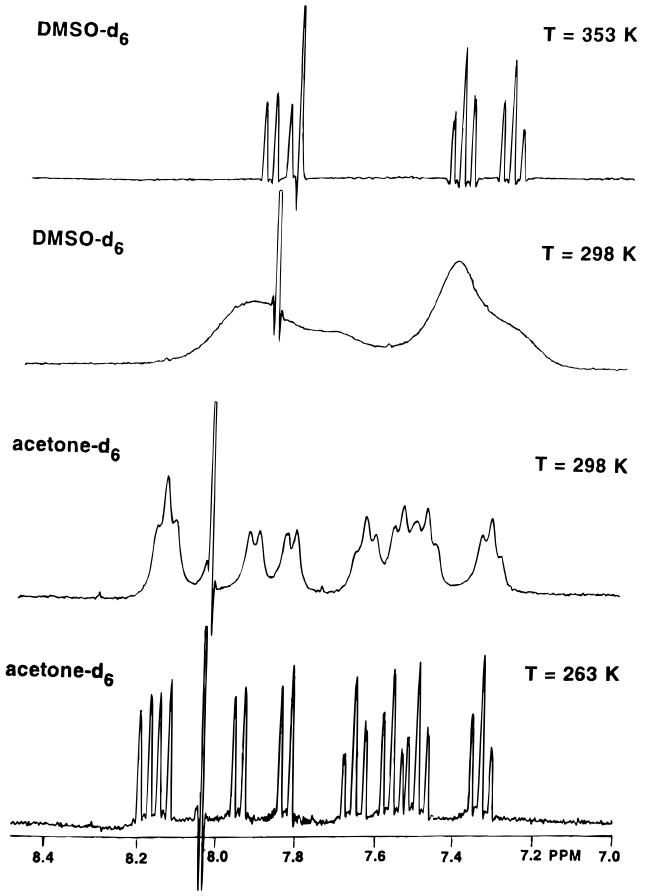


Figure 2. Variable temperature ^{1}H NMR spectra of α,α-bis-(2-benzothiazolyl)-β-(dimethylamino)ethene (**4**) (aromatic region).

for determining rate constants for methyl and heteroaryl rotation was found to be tetrachlorodeuterioethane $CDCl_2$-$CDCl_2$. The pattern assignment of the aromatic systems of **3** and **4** has been obtained from COSY NMR experiments. Data for **3** and **4** in the various solvents are shown in Table 1 for ^{1}H shift assignments and Table 2 for ^{13}C NMR data. Numbering of the systems is shown in formulas **3**−**6**. The absence of any detectable ^3J coupling between C-2 or C-2′ with the olefinic proton (H-9) prevents ring site assignments. In both cases it was not possible to distinguish between primed hydrogen and carbon atoms of one ring from those of the other one. The assignments are arbitrary, and therefore the primed set of resonances can be exchanged with those unprimed.

Enol ethers **5** and **6**, both in DMSO and in $CDCl_2$-$CDCl_2$, show anisochrony of the ring protons of the two heteroaryl moieties. No collapse was observed up to 413 K in the last solvent. No further effort was devoted to the variable temperature investigation of these compounds in view of their extreme sensitivity toward hydrolysis, particularly in the presence of trace acidity that always contaminates halogenated solvents and because the estimated barrier from MOPAC calculations (*vide infra*) was too high (ca. 25 kcal mol^{-1}). A COSY NMR experiment allowed the correct assignment to protons of enol ether **6** (Table 1). Table 2 shows ^{13}C NMR data for enol ethers **5** and **6**. Analogous to the above case of enamines **3** and **4**, it was not possible to distinguish between primed hydrogen and carbon atoms of one ring from those of the other one in **5** and **6**. Again, the assignments are arbitrary and therefore the primed set of resonances can be exchanged with those unprimed.

Enamine Tautomers of the α,α-Diheteroarylacetaldehydes. Hydrolysis of enamines **3** and **4** and of enol ethers **5** and **6** produces enamino aldehydes **7b** and **8b**. Spectroscopic evidence (^{1}H and ^{13}C NMR, IR) indicates that the enamino aldehydes are the only traceable, stable tautomers for both compounds. ^{1}H and ^{13}C NMR data are shown in Tables 1 and 2, respectively. The low solubility of both compounds, even in DMSO at 50 °C, was a limit to a thorough NMR investigation. In the ^{1}H NMR spectra the proton on C-8 is absent, and because of this, the aldehydic proton in **7b** and **8b** appears as a sharp singlet. The ^{13}C shift of C-8 is typical of an electron-rich sp^2 carbon atom and not compatible with an sp^3 hybridization. These considerations rule out structures **7c** and **8c**. The ^{13}C shift of C-9 can discriminate between tautomers **a** and **b**. In fact in both compounds **7** and **8** the shift is around 180 ppm, compatible with a conjugate carbonyl β substituted with donor atoms (e.g., in β-(dimethylamino)acrolein $\delta^{13}C_{C=O} = 189.0$ ppm[8]) and not with that of enol ethers **5** and **6** which appear 20 ppm upfield. Analogously, the proton on C-9 (around 10 ppm) is better interpreted as the shift of an aldehydic proton rather than the olefinic one of an enol. The broad ^{1}H NMR peaks at 13.9 and 14.3 ppm in **7** and **8**, respectively, exchange with D_2O and are assigned to the NH groups of the enamino aldehydes. In the IR spectra, recorded in the solid state (Nujol), only bands at 1650 and 1613 cm^{-1} are present in the region of 1600−1800 cm^{-1}. They are assigned to the carbonyls of **7b** and **8b**, respectively. We conclude that the evidence favors tautomers **b** rather than **a**, for both compounds **7** and **8**.

In the enamine **7b**, the hydrogen and carbon atoms of the two heterocyclic rings are isochronous in DMSO at room temperature. In $CDCl_3$, proton signals are somewhat broadened. In the enamine **8b**, both in DMSO and $CDCl_3$, hydrogen and carbon atoms of the two heterocyclic rings are anisochronous. They become isochronous in DMSO at 323 K. Relevant ^{1}H and ^{13}C resonances of enamino aldehydes **7b** and **8b**, dimethylamino enamines **3** and **4**, and enol ethers **5** and **6** can be compared from data reported in Chart 1.

Crystal and Molecular Structure of Enamine 4.[21] Selected molecular parameters (bond lengths and bond angles) of this compound are in Table 3. The X-ray crystal structure of the molecule is shown in Figure 3. The enamine fragment N−CH=C is coplanar with one benzothiazolyl ring, but the two heteroaryl rings are not coplanar since the average planes containing each ring present a twist angle of 73°. Therefore, in the solid state and at room temperature, conjugation develops between the enaminic nitrogen electron pool and one heterocycle only.

Variable Temperature Experiments and Activation Parameters. For both enamines **3** and **4** activation energies of two processes had to be determined, one concerning the transformation that makes isochronous the dimethylamino methyl groups ("methyl" process), the other involving the two four-^{1}H spin system of the benzene ring of the two anisochronous heterocycles ("aryl" process). To study the two four-spin aromatic systems of **3** and **4** and the methyl nonequivalence of **3**, variable temperature experiments were perfomed in $CDCl_2CDCl_2$ solution between 243 and 413 K. Spectra were recorded at 10 K intervals. Since the methyl groups

(8) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; VCH: Weinheim, 1987; p 247.

Table 1. ^{1}H NMR Shifts[a] (ppm) of Compounds 3–8

compound	*T* (K)	solvent	4	5	6	7	4′	5′	6′	7′	9	11	12
3	293	$C_2D_2Cl_4$	7.80	7.39	7.38	7.61	7.59	7.27	7.20	7.41	7.87	3.00	
	293	$CDCl_3$	7.58	7.36	7.33	7.77	7.38	7.23	7.16	7.55	7.90	3.02	
	413	DMSO-d_6	7.58	7.28	7.26	7.43					7.90	3.00	
4	293	$C_2D_2Cl_4$	8.09	7.53	7.42	7.92	7.82	7.40	7.22	7.72	7.78	2.90	
	293	$CDCl_3$	8.06	7.50	7.20	7.69	7.88	7.39	7.37	7.82	7.82	2.99	
	373	DMSO-d_6	7.91	7.42	7.30	7.85					7.84	3.00	
5	293	$CDCl_3$	7.86	7.36	7.32	7.70	7.82	7.34	7.30	7.64	8.03	4.40	1.49
	293	DMSO-d_6	7.82	7.44	7.39	7.70	7.76	7.42	7.36	7.68	8.28	4.43	1.40
	293	$C_2D_2Cl_4$	7.82	7.40	7.35	7.72	7.64	7.39	7.34	7.55	8.00	4.40	1.45
6	293	$C_2D_2Cl_4$	8.14	7.54	7.43	7.97	7.99	7.49	7.38	7.97	8.42	4.50	1.60
	293	$CDCl_3$	8.11	7.49	7.38	7.94	7.95	7.45	7.33	7.92	8.41	4.49	1.58
	293	DMSO-d_6	8.17	7.56	7.46	8.07	8.13	7.50	7.39	7.95	8.65	4.80	1.80
7	293	$CDCl_3$	7.75	7.39	7.31	7.55					9.40		
	293	DMSO-d_6	7.73	7.38	7.32	7.67					9.90		
8	293	$CDCl_3$	7.88	7.50	7.35	7.80	7.80	7.45	7.32	7.67	10.00		
	323	DMSO-d_6	8.00	7.51	7.38	8.00					9.90		

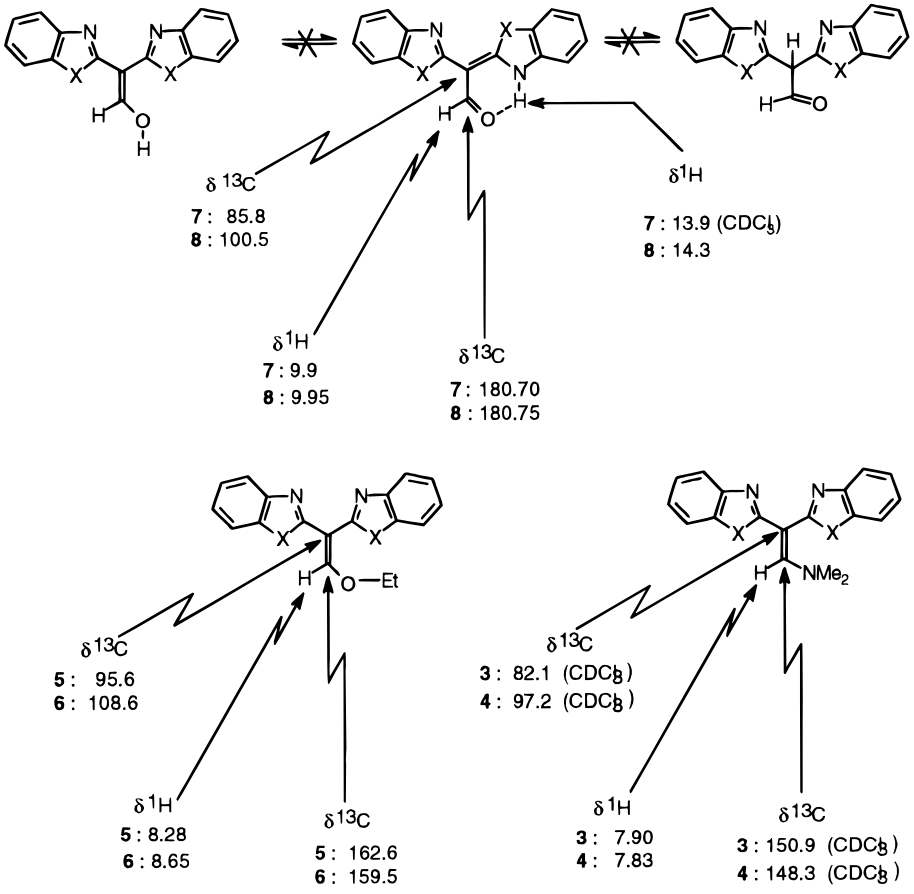
[a] Relative to Me_4Si (0.0 ppm).

Table 2. ^{13}C NMR Shifts[a] (ppm) of Compounds 3–8

compd	*T* (K)	solvent	2	4	5	6	7	7a	3a	2′	4′	5′	6′	7′	7a′	3a′	8	9	11	12
3	293	$CDCl_3$	165.3	119.7	124.6	123.9	110.6	150.6	142.5	160.1	118.1	124.1	122.8	109.6	150.3	141.6	82.1	150.9	43	
4	293	$CDCl_3$	170.4	122.9	126.0	124.9	121.0	136.3	157.6	165.0	121.5	125.8	123.2	121.0	134.1	153.7	97.2	158.3		
5	293	DMSO-d_6	160.6	119.7	125.4	124.6	110.8	149.7	141.2	157.3	119.0	124.8	124.6	110.4	149.7	141.0	95.6	162.6	72.6	15.3
6	293	DMSO-d_6	163.3	122.0	126.3	125.0	121.6	135.4	151.4	160.0	121.7	126.0	124.1	121.6	134.2	150.7	108.6	159.5	72.7	15.4
7	323	DMSO-d_6	161.4	115.8	124.6	123.6	110.1	147.0	136.0								85.8	180.7		
8	323	DMSO-d_6[b]		123.9	126.5	123.9	121.8										100.5	180.8		

[a] Relative to Me_4Si (0.0 ppm). [b] Shifts corresponding to quaternary carbons are not reported due to the low solubility of the compound in DMSO even at $T = 323$ K.

Chart 1. Comparison of Relevant NMR Shifts (ppm, in DMSO if not otherwise indicated) of 7 and 8 with Those of Enamines 3 and 4 and Enol Ethers 5 and 6



of the enamine **4** were still equivalent at 243 K, spectra had to be recorded at lower temperatures in CS_2.

The geNMR full shape analysis program[9] has been used to calculate the activation energies of the "aryl" processes of **3** and **4** and the "methyl" process of **3**. The coupling constants determined for the low-temperature spectra were maintained invariant in the simulation of high-temperature spectra. Chemical shifts of the aro-

(9) Budzelaar, P. H. M. *geNMR, NMR Simulation Program*, IvorySoft, Amsterdam, 1993.

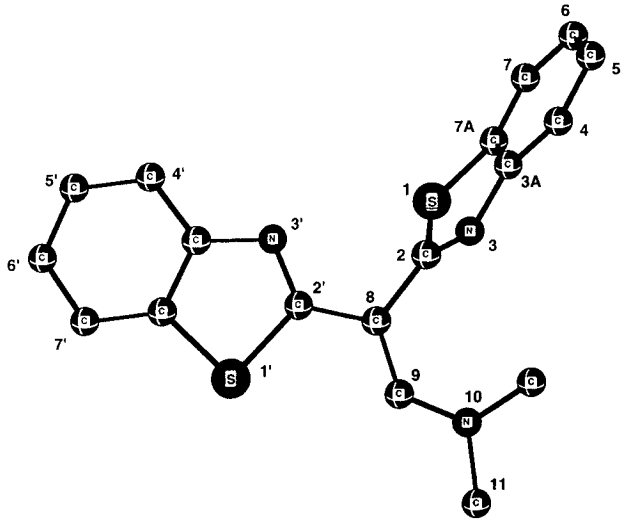


Figure 3. X-ray structure of α,α-bis(2-benzothiazolyl)-β-(dimethylamino)ethene (**4**) (hydrogen atoms are omitted).

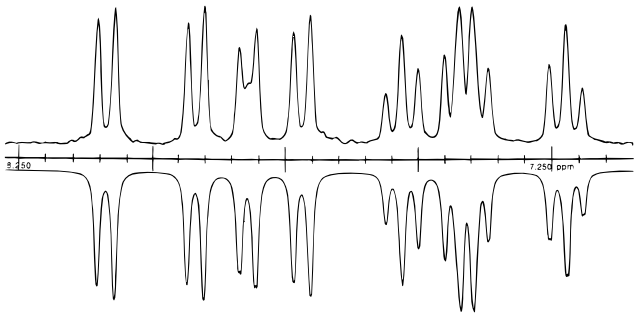


Figure 4. Experimental (top) and simulated (bottom) ^{1}H NMR spectra of α,α-bis(2-benzothiazolyl)-β-(dimethylamino)ethene (**4**) in $C_2D_2Cl_4$ at 293 K (aromatic region; the peak corresponding to the ethene hydrogen atom has been excluded from the fit).

Table 3. Selected Bond Distances (Å) and Angles (deg) for 4

Bond Lengths			
S(1)−C(2)	1.751	C(2)−N(3)	1.297
C(2)−C(8)	1.471	N(3)−C(3A)	1.389
C(3A)−C(7A)	1.397	S(1′)−C(2′)	1.769
C(2′)−N(3′)	1.299	C(2′)−C(8)	1.456
N(3′)−C(3A′)	1.386	C(8)−C(9)	1.367
C(9)−N(10)	1.334	N(10)−C(11)	1.453
Bond Angles			
C(2)−S(1)−C(7A)	89.7	S(1)−C(2)−N(3)	115.3
S(1)−C(2)−C(8)	120.1	N(3)−C(2)−C(8)	124.7
C(2)−N(3)−C(3A)	110.5	N(3)−C(3A)−C(7A)	115.9
S(1)−C(7A)−C(3A)	108.7	C(2′)−S(1′)−C(7A′)	89.3
S(1′)−C(2′)−N(3′)	114.8	S(1′)−C(2′)−C(8)	121.7
N(3′)−C(2′)−C(8)	123.5	C(2)−C(8)−C(2′)	115.0
C(2)−C(8)−C(9)	125.2	C(2′)−C(8)−C(9)	119.8
C(8)−C(9)−N(10)	131.7	C(9)−N(10)−C(11)	119.3

matic protons were slightly corrected to take into account a small temperature dependence. The corrections were performed taking as a guide the linear temperature dependence of the methine proton at C-9, a peak not directly involved in the exchange process. The actual line widths for the solvent peak were determined for each spectrum at a certain temperature. The rate constants were obtained via the best eye-fit between the experimental and the calculated spectra. Figure 4 shows an example of the fit for the aromatic portion of enamine **4**. The Eyring equation (1) was used to obtain $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$. The plot of ln(k/T) vs 1/T shows a good linearity

Table 4. Experimental Activation Parameters for Enamines 3 and 4 and Computed Values for Models 9−12

compd	source	value[a]	arom[b]	methyl[b]
3	eq 1[c]	$\Delta H^{\ddagger}$	21.02 ± 0.72	12.85 ± 1.01
		$\Delta S^{\ddagger}$	4.52 ± 0.27	−0.99 ± 0.28
		$\Delta G^{\ddagger}$	19.65 ± 0.73	13.15 ± 1.01
	eq 2[d]	$\Delta G^{\ddagger}$		12.97
4	eq 1[c]	$\Delta H^{\ddagger}$	10.78 ± 0.90	
		$\Delta S^{\ddagger}$	−20.11 ± 0.31	
		$\Delta G^{\ddagger}$	16.77 ± 0.91	
	eq 2[e]	$\Delta G^{\ddagger}$		8.71
9	gas phase	$\Delta H^{\ddagger}$	21.71	
	COSMO 5[f]	$\Delta H^{\ddagger}$	17.01	
	COSMO 10[f]	$\Delta H^{\ddagger}$	15.86	
10	gas phase	$\Delta H^{\ddagger}$	17.27	
	COSMO 5[f]	$\Delta H^{\ddagger}$	12.19	
	COSMO 10[f]	$\Delta H^{\ddagger}$	10.54	
11	COSMO 5[f]	$\Delta H^{\ddagger}$	ca. 26	
12	COSMO 5[f]	$\Delta H^{\ddagger}$	ca. 25	

[a] Values of $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ are reported in kcal mol^{-1}, values of $\Delta S^{\ddagger}$ in cal mol^{-1} K^{-1}. [b] For "aromatic" and "methyl" processes, see text. [c] Experimental values for $CDCl_2CDCl_2$ solutions, performing full shape analysis with geNMR. [d] Experimental value in $CDCl_3$ solution. [e] Experimental value in CS_2 solution. [f] COSMO 5 calculations assume for the solvent $\epsilon = 5$; COSMO 10, $\epsilon = 10$.

for the "aryl" process of **4** ($n = 10$, $r^2 = 0.994$) and for the "methyl" process of **3** ($n = 7$, $r^2 = 0.998$).

$$\ln(k/T) = \ln(\kappa k_B/h) + \Delta S^{\ddagger}/R - \Delta H^{\ddagger}/RT \qquad (1)$$

The analogous plot for the "aryl" process of **3** shows some curvature over the total of $n = 7$ points. A straight line is obtained for the first four points at a lower temperature ($n = 4$, $r^2 = 0.990$). Activation parameters obtained by the geNMR full shape analysis are shown in Table 4. Since the activation energy $\Delta G^{\ddagger}$ for the "methyl" process of enamine **4** could not be obtained in $CDCl_2CDCl_2$, variable temperature experiments were performed in CS_2. The lowest temperature compatible with sufficient solubility for recording ^{1}H NMR spectra of this compound in this and other solvent mixtures was about 180 K. In CS_2 at 193 K, the methyl groups show a broad singlet that splits at 180 K into two broad (line width ca. 35 Hz) peaks separated by 168 Hz. The value of $\Delta G^{\ddagger} = 8.71$ kcal mol^{-1} (Table 4) is obtained by assuming a coalescence temperature T_C of 190 K and applying eq 2.[10]

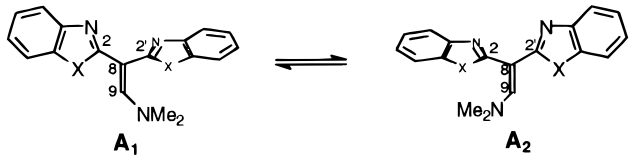
$$\Delta G^{\ddagger}\ (\text{kcal mol}^{-1}) = (4.575 \times 10^{-3})T_C[9.97 + \log(T_C/\Delta\nu)] \qquad (2)$$

To assess the validity of the value obtained by this procedure for enamine **4**, we determined the value for the "methyl" process of enamine **3** in terms of the $\Delta G^{\ddagger}$ value obtained with the geNMR full shape analysis compared to the value obtained by applying eq 2. Relevant data to be inserted in eq 2 for enamine **3** are based on the observation that peaks of the dimethylamino group are sharp singlets (separated by 164.1 Hz) in $CDCl_3$ at 243 K, coalescing at 278 K. Using these values and applying eq 2, we obtained a value of $\Delta G^{\ddagger} = 12.97$ kcal mol^{-1}, in excellent agreement with the figure of 13.15 kcal mol^{-1} obtained by the geNMR procedure.

Semiempirical Calculations. Spectroscopic isochrony of the two heteroaryl rings in **3** and **4** is obtained

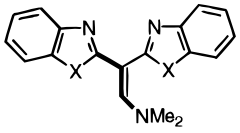
(10) Günther, H. *NMR Spectroscopy. An Introduction*; J. Wiley and Sons: Chichester, 1980; p 247.

Scheme 1

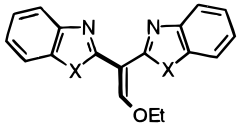


A_1 A_2

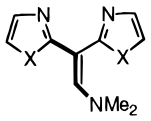
when the equilibrium of Scheme 1 is fast on the NMR time scale. This process involves rotation along three bonds: C-8−C-9, C-2−C-8, and C-2′−C-8. The two conformers $\mathbf{A_1}$ and $\mathbf{A_2}$ represent two minimum energy geometries on an energy map and are connected along the reaction coordinate through the saddle point, characterized by a stationary geometry. We used the program MOPAC[11] to calculate energies and geometries of the system in the ground state, along the trace, and at the saddle point. The PM3 semiempirical Hamiltonian was used for all the calculations. Because of the large number of atoms of **3**−**6**, the gradient remained relatively high in the energy calculations. For this reason and wishing to obtain smaller gradients, we assumed that the simplified molecules **9** and **10**, in which the benzo-fused



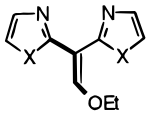
3a : X = O
4a : X = S



5a : X = O
6a : X = S



9 : X = O
10 : X = S



11 : X = O
12 : X = S

rings have been eliminated, could represent good models for **3** and **4**. Indeed, much better gradients were obtained in the energy calculations of **9** and **10**, and in view of the close electronic similarity of **3** with **9** and of **4** with **10**, the trend of the *relative* barriers of **9** and **10** is believed to mimic in a sufficiently close manner that of **3** and **4**. An analogous approach was followed for systems **5** and **6** vs **11** and **12**.

The transition state should be the one with the maximum energy along the trace. To locate this transition state, we calculated the energies of the systems by varying between 0° and 180° the dihedral angle connecting one heteroaryl ring and the dimethylamino group (bold bonds in formulas **3a**−**6a** and **9**−**12**). The structure with the maximun energy content, presenting a dihedral angle of 90°, was refined with one of the optimization methods (keyword = TS) that can minimize the energy at the plateau without searching for a minimum energy geometry. Once the stationary geometry was found, the transition state should be characterized by calculating the vibrational frequencies for the molecule and verifying that there was one (and only one) imaginary frequency that corresponds to a negative force constant. Unfortunately, we could not find the correct frequency because the saddle points are very flat and the program found it

(11) Stewart, J. J. P. MOPAC 6.0, 1990, QCPE Program 455.

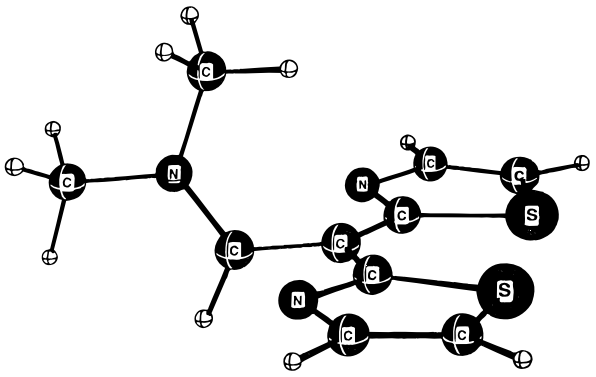


Figure 5. Calculated (PM3) structure of the transition state of enamine **10** corresponding to the "aryl" rotational process (see text).

difficult to recognize the maximum energy corresponding to the transition states. However, we considered the optimized geometries and corresponding energies to be very close to those of the transition state. Energy barriers for **9**−**12** are shown in Table 4.

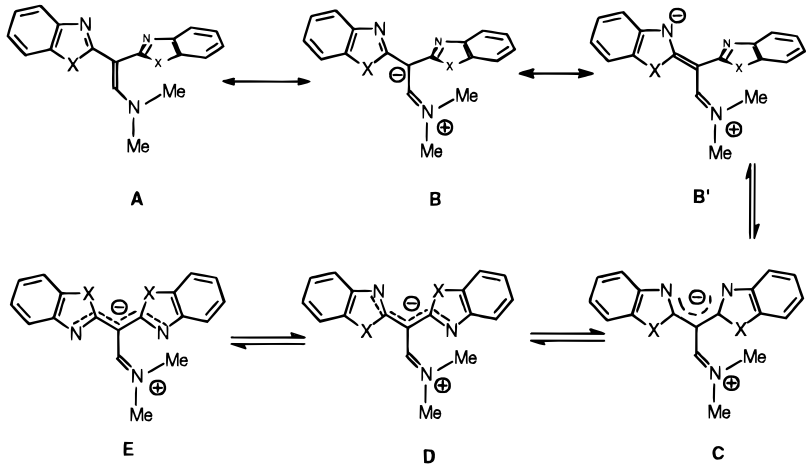
Solvent effects on the computed energy barriers were simulated using the COSMO (COnductor-like Screening MOdel) option, developed by Klamt and Schüürmann.[12] It assumes that the medium is a conductor and approximates the dielectric energy by the method of image charges. The method requires the dielectric constant of the solvent and the effective solvent radius to be specified. The value of the trust solvent radius (2.90 Å) was found by calculating the van der Waals area for 1,1,2,2-tetrachloroethane. Entries reported in Table 4 as COSMO 5 and COSMO 10 have assumed for the medium a dielectric constant of $\epsilon = 5$ and $\epsilon = 10$, respectively.

Results of the calculations are relevant. The ground state geometry of **9** and **10** and of **11** and **12** show that one heteroaryl ring is twisted relative to the plane identified by C(2)−C(8)−C(2′) by 85° in **9**, 77° in **10**, 82° in **11**, and 82° in **12** (gas phase). A very good correlation was obtained between the calculated torsional angle in **10** (77°) and the corresponding value from the X-ray structure of **4** (73°). Moreover, calculations show that coplanarity of the two heteroaryl rings with the C-8−C-9 double bond is reached at the transition state. The common feature of the transition states of all of the molecules examined is the fact that the oxygen or the sulfur atoms, instead of the nitrogen atoms, are directed toward the same region of the space, as can be seen in Figure 5, which defines the conformation of compound **10** at the transition state. The key attribute that selectively discriminates the sulfur set from the oxygen series is the short S···S distance (3.05 and 2.94 Å for $\epsilon =$ 5 and 10, respectively, for compound **10** at the transition state) between the two heterocycles of the same molecule, suggesting a stabilizing interaction between these two atoms (van der Waals radii of S = 1.85 Å). Instead, the distance between the oxygen atoms in the oxygen series is comparable with the sum of van der Waals radii (O···O distance equal to 2.80 and 2.75 Å for $\epsilon = 5$ and 10, respectively, for compound **9** at the transition state).

Calculations performed on enol ethers **11** and **12** show that the energy barriers may be too high to be reached experimentally by the ^{1}H NMR technique. For this reason and because **5** and **6** are vulnerable to trace

(12) Klamt, A.; Shüürmann, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 799.

Scheme 2



humidity, especially at high temperatures, we did not investigate their experimental energy barriers.

Discussion

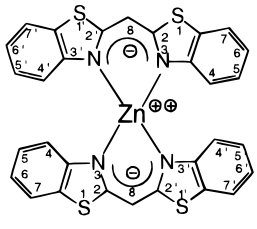
The rank of the electron-withdrawing capacity of heterocycles, obtained by the charge demand approach on carbanions of **1** and **2**, and the results obtained by the evaluation of energy barriers corresponding to the "aryl" rotational process (see Scheme 1) in enamines **3** and **4** are coherent in assigning a higher value to the 2-benzothiazolyl group. The "aryl" rotational process is easier in enamine **4** than in its oxygen counterpart **3**, and this is certainly associated with the greater stability of the limit dipolar structure **E** reached at the saddle point (Scheme 2). In addition to the stabilization associated with the electronic effect of the benzothiazole ring, the short S···S bond distance at the transition state is suggestive of a stabilizing interaction contributing to decreasing the enthalpy term $\Delta H^{\ddagger}$. This interaction is also responsible for the negative entropy contribution $\Delta S^{\ddagger}$, at variance with the positive value of the benzoxazolyl enamine **3**, as usually expected for rotational processes. A higher order is thus required in the transition state for the benzothiazolyl derivative. Short S···S distances, suggestive of partial bonding involving tricoordinated tetravalent sulfur atoms, have been suggested[13] and ascertained by X-ray investigations in a number of thione derivatives of 1,2- and 1,3-dithiole compounds.

The computational result appears reliable in view of the success obtained in reproducing molecular parameters of enamine **4** in the crystal. Enamine **4** at room temperature can be conveniently represented by the limit formulas **A**−**B** of Scheme 2. It appears that the contribution of **B** is particularly important. It is instructive to compare (Table 5) some relevant bond distances in **4** with those of the neutral zinc chelate **13**[14] in which the bis(2-benzothiazolyl)methane residue is present as a carbanionic ligand, whose bond lengths are reported as a model for a fully delocalizated system. In the enamine

Table 5. Relevant Bond Distances (Å) in 4 and 13

bond	**4**	**13**
S(1)−C(2)	1.751	1.749
S(1′)−C(2′)	1.769	1.756
C(2)−N(3)	1.299	1.328
C(2′)−N(3′)	1.297	1.337
C(2)−C(8)	1.471	1.387
C(2′)−C(8)	1.456	1.391
C(8)−C(9)	1.367	
C(9)−N(10)	1.334	

4, the 9−10 distance, shorter than a single C(sp^2)−N bond, and the 8−9 distance, somewhat longer than a C=C double bond, are suggestive of the delocalization of the dimethylamino nitrogen atom electron pool as in the limit structure **B** of Scheme 2. Indeed the 2′−8 distance, involving the benzothiazolyl ring that is coplanar and conjugate with the enaminic fragment, is shorter than the 2−8 distance involving the twisted benzothiazolyl ring. However, such a delocalization does not appear to include the C=N bonds 2−3 and 2′−3′ of the heterocycles. The 2−3 and 2′−3′ distances in **4** are much shorter and, correspondingly, the 2−8 and 2′−8 are much longer than in **13**. Therefore, enamine delocalization



13

does not involve the heterocyclic ring, leading to the conclusion that indeed the limit structure **B**, rather than **B′**, better describes the ground state conjugation in enamine **4**. These results indicate that the generally accepted analogies according to which enamines are ground state models for carbanions should be critically evaluated case by case.

The lower rotational barrier for the "methyl" process in enamine **4**, with respect to the corresponding one in enamine **3**, is apparently in contrast with the higher electron-withdrawing capacity of the 2-benzothiazolyl group. A close evaluation of literature data of push-pull ethylenes shows that this is not the case. In fact, while the rotational energy barrier along the double bond of

(13) (a) Klingsberg, E. *J. Org. Chem.* **1966**, *31*, 3489−3493. (b) Klingsberg, E. *J. Heterocycl. Chem.* **1966**, *3*, 243−243. (c) Klingsberg, E. *Chem. Ind.* **1968**, *51*, 1813−1814. (d) Stavaux, M.; Lozac'h, N. *Bull. Soc. Chim. Fr.* **1968**, *10*, 4273−4274. (e) Stavaux, M. *Bull. Soc. Chim. Fr.* **1971**, *12*, 4429−4434. (f) Klingsberg, E. *J. Org. Chem.* **1972**, *37*, 3226−3229. (g) Kristensen, R.; Sletten, J. *Acta Chem. Scand.* **1973**, *27*, 2517−2523.

(14) Abbotto, A.; Alanzo, V.; Bradamante, S.; Pagani, G. A.; Rizzoli, C.; Calestani, G. *Gazz. Chim. Ital.* **1991**, *121*, 365−368.

enamines is directly related to the electron-withdrawing strength of the β substituent(s),[6a] the rotational process involving the C−N bond is somewhat more complicated. Indeed, the data show that the energy barrier along this bond is not linearly related with the σ_R^- values of the β substituent(s). A significant example is represented by the rotational energy barrier along the C−N bond in *trans* $XCH{=}CHNR_2$ systems, where X = C(O)R and CO_2R.[15] Although C(O)R is noticeably a stronger electron-withdrawing group than CO_2R, the energy barrier for the former is lower, in contrast with an expected higher double bond character for the C−N bond. Small sensitivity and steric factors are, among the others, responsible for the lack of a linear dependence on the electron-withdrawing capacity of β substituents. In enamine **4** the sulfur atom of the benzothiazolyl ring is likely involved in a higher steric interaction—with respect to enamine **3**—with the methyl of the amino group, interaction which is released at the transition state of the rotational "methyl" process.

Another important result that merits assessment is the unprecedented isolation of the NH-enamines **7b** and **8b**, where tautomerization involves the benzoxazolyl and benzothiazolyl rings, respectively. The tautomeric enaminic structure presented by compounds **7** and **8** is evidence of the strong electron-withdrawing capacity of the heterocyclic substituents. Enamine tautomers of bis(2-benzothiazolyl)methane derivatives have been identified[16] by NMR, UV, and IR spectroscopies as species in equilibrium whith their CH analogs but have never been isolated in a pure state. Intermediacy of enamine tautomers of bis(2-benzothiazolyl)methane derivatives has been invoked in the photooxidation of these compounds.[17] Alternatively, enaminone tautomers of 2-acylazines, where the NH-enaminic moiety is incorporated in the heterocyclic ring, were found to exist, and sometimes predominate, in the equilibrium with the enol and the keto forms.[18] These findings suggest that the exceptional stability of enamines **7b** and **8b** is a consequence of the presence of three strong electron-withdrawing substituents on the same carbon atom, resulting in a destabilization of structures **7c** and **8c**. On considering that the charge demand of the 2-benzothiazolyl group is intermediate between that of the acetyl and methoxycarbonyl groups,[2] it is quite expected that NH tautomers of bis(2-benzothiazolyl)methane are spectroscopically traceable and not isolable (like instead are the enols of β-dicarbonyl compounds), but less elusive than the enols of malonic esters. The preference for the enamine forms **7b** and **8b**, rather than the enols **7a** and **8a**, respectively, is likely due to the formation of a tetrasubstituted rather than a trisubstituted ethene derivative.

In conclusion, the 2-benzothiazolyl and 2-benzoxazolyl groups are confirmed as strong electron-withdrawing substituents. In methanes trisubstituted with electron-withdrawing groups, these substituent tautomerize to the corresponding NH-enamines. The 2-benzothiazolyl substituent is more electron-withdrawing than its oxygen analog: this is confirmed by both the charge demands and the dynamic NMR approach. Nonbonded stabilizing S···S interactions of tricoordinated sulfur atoms are evidenced not only in ground states as previously documented but also in rotational transition states.

Experimental Section

For preparative purposes, ^{1}H NMR spectra were recorded on a Bruker AC-300 instrument operating at 300 MHz, or Bruker AMX 500 WB operating at 500 MHz, using Me_4Si as external standard. ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer, operating at 75.47 MHz; shifts were measured relative to Me_4Si. Coupling constant values, *J*, are given in hertz. The ^{1}H NMR spectra used to determine the rotational rate constants were recorded on a Bruker AM 250 and a Bruker WM 500. Elemental analyses were performed on a Perkin-Elmer 240 instrument by the microanalysis laboratory of our department. Melting points are uncorrected. Anhydrous DMF was stored over molecular sieves. Extracts were dried over Na_2SO_4. Bis(2-benzothiazolyl)methane (**2**)[19] and bis(2-benzoxazolyl)methane (**1**)[20] were prepared according to the literature.

Condensation of Bis(2-benzoxazolyl)methane (1) with *N,N*-Dimethylformamide Dimethyl Acetal: α,α-Bis(2-benzoxazolyl)-*β*-(dimethylamino)ethene (3). A solution of bis(2-benzoxazolyl)methane (1.25 g, 5.0 mmol) in anhydrous DMF (15 mL) was added dropwise under nitrogen to a stirred solution of *N,N*-dimethylformamide dimethyl acetal (1.79 g, 15.0 mmol) in anhydrous DMF (5 mL) at 120 °C. The reaction mixture was stirred at 120 °C for 10 h, cooled to room temperature, poured onto ice (100 mL), and extracted with CH_2Cl_2 (5 × 40 mL). The dried organic extracts were evaporated to dryness to give the crude compound **3** as a red oil which was purified by chromatography (flash) on silica gel (CH_2Cl_2−AcOEt, 4:1) to give a yellow oil (0.736 g, 48.2%). An analytical sample was obtained from a toluene solution by precipitation with hexane, mp 105−108 °C. Anal. Found: C, 70.62; H, 4.91; N, 13.91. Calcd for $C_{18}H_{15}N_3O_2$: C, 70.79; H, 4.95; N, 13.77. For ^{1}H and ^{13}C NMR spectra, see Tables 1 and 2, respectively. MS (EI): *m/z* 305 (M^+, 100), 198 (50), 149 (100), 120 (82).

Condensation of Bis(2-benzothiazolyl)methane (2) with *N,N*-Dimethylformamide Dimethyl Acetal: α,α-Bis(2-benzothiazolyl)-*β*-(dimethylamino)ethene (4). A solution of bis(2-benzothiazolyl)methane (0.50 g, 1.76 mmol) in anhydrous DMF (10 mL) was added under nitrogen and dropwise to a stirred solution of *N,N*-dimethylformamide dimethyl acetal (0.21 g, 1.76 mmol) in the same solvent (5 mL). A deep blue color formed immediately. The reaction mixture was stirred for 4 h at 100 °C, cooled, and poured onto ice (150 mL). The aqueous purple solution was extracted with CH_2Cl_2 (4 × 25 mL), and the deep red organic phase was washed with water (6 × 50 mL), dried, and evaporated to dryness to give a dark oil which was submitted to chromatography (flash) on silica gel (CH_2Cl_2−AcOEt, 4:1) to separate the desired product from the deep colored byproduct. The isolated yellow solid was taken up with petroleum ether to give the compound **4** as a light yellow solid (0.20 g, 0.59 mmol, 34%), mp 154−156 °C. Anal. Found: C, 64.12; H, 4.45; N, 12.62. Calcd for $C_{18}H_{15}N_3S_2$: C, 64.08; H, 4.48; N, 12.46. For ^{1}H and ^{13}C NMR spectra, see Tables 1 and 2, respectively.

Condensation of Bis(2-benzoxazolyl)methane (1) with Ethyl Orthoformate: α,α-Bis(2-benzoxazolyl)-*β*-ethoxyethene (5). A mixture of bis(2-benzoxazolyl)methane (1.00 g, 4.00 mmol), ethyl orthoformate (0.890 g, 6.00 mmol), and Ac_2O (3.00 g, 29.4 mmol) was heated at 130 °C for 30 min while distilling off the ethyl acetate formed. The solution was

(15) Reference 6a, p 155.

(16) (a) Ramos, M. T.; Avendaño, C.; Elguero, J.; Jimeno, M. L.; Bellanato, J.; Florencio, F.; Aparicio, J. S. *Heterocycles* **1989**, *29*, 165−181. (b) Avendaño, C.; Ramos, M. T.; Elguero, J.; Jimeno, M. L.; Bellanato, J.; Florencio, F. *Can. J. Chem.* **1988**, *66*, 1467−1473.

(17) Ramos, M. T.; Avendaño, C.; Elguero, J.; Jimeno, M. L. *Bull. Soc. Chim. Belg.* **1989**, *98*, 497−501.

(18) (a) Mondelli, R.; Merlini, L. *Tetrahedron* **1966**, *22*, 3253−3273. (b) More O'Ferrall, R. A.; Murray, B. A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2461−2470.

(19) Rai, C.; Braunwarth, J. B. *J. Org. Chem.* **1961**, *26*, 3434.

(20) Rai, C.; Braunwarth, J. B. U.S Patent 3,250,780; *Chem. Abstr.* **1966**, *65*, 7180g.

(21) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

evaporated to dryness to give a dark yellow oil, which was taken up with water (10 mL) and CH_2Cl_2 (10 mL). The separated organic phase was dried and evaporated to dryness to give crude α,α-bis(2-benzoxazolyl)-β-ethoxyethene (**5**) which, purified by flash chromatography (silica gel, CH_2Cl_2−AcOEt, 5:1), led to the product as a yellowish semisolid oil (0.83 g, 2.71 mmol, 68%). An analytical solid sample, mp 87−89 °C, was obtained by treating the oil with petroleum ether. Anal. Found: C, 70.38; H, 4.96; N, 9.67. Calcd for $C_{18}H_{14}N_2O_3$: C, 70.57; H, 4.61; N, 9.15. For ^1H and ^{13}C NMR spectra, see Tables 1 and 2, respectively. MS (EI): *m*/*z* 306 (M^+, 100), 277 (67), 250 (100). The product must be stored in a dry atmosphere. It is readily hydrolyzed to **7b** when kept in the air or when dissolved in nonanhydrous solvents.

Enaminic Tautomer of α,α-Bis(2-benzoxazolyl)acetaldehyde (7b). To carry out the hydrolysis, the crude α,α-bis-(2-benzoxazolyl)-β-ethoxyethene (**5**) (0.20 g, 0.65 mmol) was dissolved in EtOH (5 mL), and 3 drops of 10% hydrochloric acid were added. After stirring at room temperature for 2 h, the enaminic tautomer of α,α-bis(2-benzoxazolyl)acetaldehyde (**7b**) was obtained as a yellow precipitate (0.14 g, 0.50 mmol, 77%), mp 245 °C. A sample was dissolved in MeOH containing some 30% aqueous NH_3, and then the solution was filtered and neutralized with 20% hydrochloric acid to give analytically pure compound **7b**, mp 245 °C. Anal. Found: C, 68.85; H, 3.81; N, 10.11. Calcd for $C_{16}H_{10}N_2O_3$: C, 69.05; H, 3.62; N, 10.07. For ^1H and ^{13}C NMR spectra see Tables 1 and 2, respectively. The same compound **7b** can be obtained by hydrolytic cleavage of the enamine **3** under analogous conditions (AcOH and catalytic amounts of hydrochloric acid).

Condensation of Bis(2-benzothiazolyl)methane (2) with Ethyl Orthoformate: α,α-Bis(2-benzothiazolyl)-β-ethoxyethene (6). A mixture of bis(2−benzothiazolyl)-methane (1.00 g, 3.54 mmol), ethyl orthoformate (0.785 g, 5.30 mmol), and Ac_2O (3.00 g, 29.4 mmol) was heated at 130 °C for 30 min while distilling off the ethyl acetate formed. The solution was evaporated to dryness to give a brown oil which was taken up with water (10 mL) and CH_2Cl_2 (10 mL). The separated organic phase was dried and evaporated to dryness to give the crude α,α-bis(2-benzothiazolyl)-β-ethoxyethene (**6**) (1.05 g, 3.10 mmol, 88%) as a red brown semisolid glassy viscous oil. An analytical solid sample, mp 96−98 °C, was obtained by treating the oil with petroleum ether. Anal. Found: C, 63.70; H, 4.43; N, 8.43. Calcd for $C_{18}H_{14}N_2OS_2$: C, 63.89; H, 4.17; N, 8.28. For ^1H and ^{13}C NMR spectra, see Tables 1 and 2, respectively. MS (EI): *m*/*z* 338 (M^+, 100), 309 (100), 282 (100). The product must be kept in a dry atmosphere. It is readily hydrolyzed to the enamine **8b** when kept in the air or when dissolved in nonanhydrous solvents.

Enaminic Tautomer of α,α-Bis(2-benzothiazolyl)acetaldehyde (8b). To carry out the hydrolysis, the crude α,α-bis(2-benzothiazolyl)-β-ethoxyethene (**6**) (0.36 g, 1.06 mmol) was dissolved in EtOH (5 mL), and the solution was treated with 4 drops of 10% hydrochloric acid. The immediate formation of a precipitate was observed. The reaction mixture was stirred for 30 min at room temperature. The light brown solid was filtered to give the crude enaminic tautomer of α,α-bis(2-benzothiazolyl)acetaldehyde (**8b**) (0.24 g, 0.77 mmol, 73%), mp 220 °C. An analytical sample was obtained by dissolving the product in MeOH containing some 30% aqueous NH_3, filtering the solution, and neutralizing with 20% hydrochloric acid, mp 220 °C. Anal. Found: C, 62.22; H, 2.98; N, 9.13. Calcd for $C_{16}H_{10}N_2OS_2$: C, 61.93; H,3.25; N, 9.03. For ^1H and ^{13}C NMR spectra, see Tables 1 and 2, respectively.

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