

# Rotational Isomerism of *N,N'*-Dimethyl-*N,N'*-diacyl-1,2-diaminoethanes and Their Thio Analogues as Studied by $^1\text{H}$ and $^{13}\text{C}$ NMR and by Molecular Mechanics

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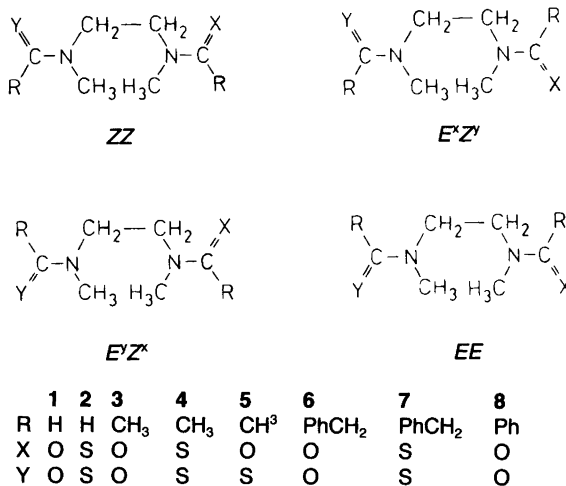
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The *anti-gauche* conformational distribution with respect to the  $\text{CH}_2\text{—CH}_2$  bond in a series of *N,N'*-dimethyl-*N,N'*-di(thio)acyl-1,2-diaminoethanes has been studied using the sum of the  $^3J_{\text{HH}}$  values obtained from the  $^{13}\text{C}$  satellite spectra in the  $^1\text{H}$  NMR spectra, and in one case, using a "mixed" amide-thioamide, from the  $^1\text{H}$  NMR spectrum. It was concluded that the dominance of *ZZ* forms with respect to the (thio)amide bonds is not entirely due to a strong stabilization of the *gauche* forms except for the *N,N'*-diformyl compounds. Molecular mechanics calculations (MM2) predict stabilization of the *ZZ*, *gauche* form by dipole-dipole attraction but also indicate the general importance of non-bonded interactions in determining the conformational equilibria. The solvent dependence of the equilibria was studied by measurements in  $\text{CDCl}_3$  and acetone- $d_6$ , and a general decrease in population of the *ZZ* form with increasing solvent polarity was observed; however, the effect of solvent on the *anti-gauche* equilibria was less clear-cut.

In a previous paper,<sup>1</sup> the composition of a number of *N,N'*-dimethyl-*N,N'*-diacyl-1,2-diaminoethanes and thio analogues in terms of the configuration (*EE*, *EZ*, or *ZZ*) with respect to the C–N partial double bond of the (thio)amide groups was analyzed on the basis of  $^1\text{H}$  NMR spectra, and the general preponderance of the *ZZ* isomers and the low population of the *EE* forms was rationalized by molecular mechanics calculations, using the Allinger MM1 force field,<sup>2</sup> on two representative diacyl compounds. The preponderance of the *ZZ* forms was explained by a combination of steric and dipole attraction effects, which also favoured the *gauche* over the *anti* form.

As a continuation and extension of the earlier work we now present the results of a study in which direct experimental evidence concerning the conformational distribution in the  $\text{CH}_2\text{—CH}_2$

fragment has been obtained by use of  $^1\text{H}$  NMR measurements at higher frequency (250–300 MHz). The compounds studied are those de-



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scribed in Ref. 1 (1–4 and 6–8), together with a “mixed” amide-thioamide (5) with two *EZ* forms (designated  $E^OZ^S$  and  $E^SZ^O$ ).

Results from  $^{13}\text{C}$  NMR measurements and molecular mechanics calculations using an improved force field (MM2)<sup>3</sup> are also included.

## Experimental

**Preparations.** The methods used to prepare compounds 1–4 and 6–8 are described in Ref. 1. *N*-Acetyl-*N'*-thioacetyl-*N,N'*-dimethyl-1,2-diaminoethane (5) was obtained by reaction of 4 with one equiv. of MeI in acetone/ether to give the mono-methiodide of 4 as a colourless, non-crystalline material. Reaction of this with an excess of 10% aqueous  $\text{NaHCO}_3$  at 50°C led to evolution of MeSH and the formation of a colourless, non-crystalline product, from which 5 was obtained as

colourless prisms, m.p. 77–78°C, in 50% yield after chromatography on silica with toluene as the mobile phase. The purity of the product was ascertained by TLC, and its identity follows from the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra (*vide infra*).

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded with Bruker WM-250 and Varian XL-300 pulsed FT spectrometers operating at 250.1 and 299.9 MHz for  $^1\text{H}$  and at 62.9 and 75.4 MHz for  $^{13}\text{C}$ , respectively, and at ambient temperature (ca. 300 K). The 2D  $^1\text{H}$ - $^{13}\text{C}$  NMR correlation (Fig. 1) was obtained by using the standard Varian HETCOR software. The populations (*p*) of the *ZZ*, *EZ* and *EE* forms were determined by integration of the  $^1\text{H}$  NMR spectrum (Fig. 1, top).

*Molecular mechanics calculations* on compounds 1, 3, 4 and 5 were performed using the Allinger 1977 force field, with non-standard parameters

Table 1. Populations (mole fractions) of the conformers about the C(X)–N bond (*p*) and of the *anti* form about the  $\text{CH}_2$ – $\text{CH}_2$  bond ( $n_a$ ) at 303 K.

Compound	Solvent <sup>a</sup>	<i>ZZ</i>			<i>EZ</i>			<i>EE</i>		
		<i>p</i>	$N^b$	$n_a$	<i>p</i>	<i>N</i>	$n_a$	<i>p</i>	<i>N</i>	$n_a$
1	C	0.42	10.48	0.00	0.46	10.22	0.00	0.12	11.30	0.11
	A	0.25	10.60	0.02	0.50			0.25	13.90	0.46
2	C	0.73			0.24	12.80	0.31	0.03		
	A		11.69	0.16						
3	C	0.56	12.06	0.21	0.22			0.22	12.97	0.34
	A		14.62	0.56						
4	C	0.68	13.68	0.43	0.30	13.19	0.37	0.02		
	A	0.34	13.52	0.41	0.48	14.01	0.48	0.07	13.70	0.43
5	C	0.60	13.18	0.36	0.15 <sup>c</sup>	13.43	0.40	≤ 0.05		
					0.20 <sup>d</sup>	13.43	0.40			
	A	0.40	12.57	0.28	0.25 <sup>c</sup>	13.92	0.46	0.08	12.45	0.27
					0.27 <sup>d</sup>	13.55	0.41			
6	C	0.58			0.39			0.03		
	A	0.24	10.78	0.04	0.41	13.41	0.39	0.35	11.88	0.19
7	C					14.56	0.55			
	A	0.31	13.85	0.45	0.63	14.15	0.49	0.06		
8	C <sup>e</sup>	0.70	13.52	0.41	0.20			0.10		
	A		10.23	0.00						

<sup>a</sup>C =  $\text{CDCl}_3$ , A =  $(\text{CD}_3)_2\text{CO}$ . <sup>b</sup> $N = J + J'$  (Hz). <sup>c</sup> $E^OZ^S$ . <sup>d</sup> $E^SZ^O$ . <sup>e</sup>In a paper published after Ref. 1, Cirrioncione *et al.*<sup>6</sup> reported only one rotamer (>95%) for 8 in  $\text{CDCl}_3$ , which they originally assigned as the *EE* form. After discussions between the research groups it was agreed that our earlier results were correct, and our new measurements in this study essentially confirm these views.

for the amide group taken from Ref. 1 and for the thioamide group from Ref. 4. Several starting geometries were constructed for each molecule using the program MOLBUILD,<sup>5</sup> with the option of constructing conformational energy maps using simultaneous rigid rotations about the two CH<sub>2</sub>-N bonds.

## Results

The <sup>1</sup>H chemical shifts of compounds 1-4 and 6-8 in CDCl<sub>3</sub> have been reported previously.<sup>1</sup> <sup>1</sup>H NMR spectra also recorded in acetone-*d*<sub>6</sub> for the purpose of studying the effect of a more polar solvent on the conformer distribution. Rather small solvent effects on the chemical shifts were observed (≤0.1 ppm on going from CDCl<sub>3</sub> to

acetone-*d*<sub>6</sub>), whereas the effects on the conformational distribution with respect to the (thio) amide bond (*ZZ*, *EZ* and *EE*; slow rotation at ambient temperature) were notable (Table 1).

We have attempted to obtain a measure of the time-averaged conformer distribution with respect to the central C-C bond (*anti-gauche*) from the vicinal coupling constants obtainable, in principle, from the <sup>13</sup>CH<sub>2</sub> satellites in the <sup>1</sup>H NMR spectra.<sup>‡</sup> However, this attempt was hampered by the degeneracy observed for the AA'BB'X systems. For most of the systems, the <sup>13</sup>CH<sub>2</sub> satellite signals were close to triplets. Nevertheless, it was possible in most cases to estimate, with some

‡ For the unsymmetrical compound 5, directly from the <sup>1</sup>H spectrum.

Table 2. <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts (ppm) for the C-N rotamers of compounds 3, 4 and 5.

Compd.	Solvent	Nucl.	Form	CH <sub>3</sub> C		CH <sub>3</sub> N		CH <sub>2</sub> N		C=O	C=S
				O <sup>a</sup>	S <sup>a</sup>	O	S	O	S		
3	CDCl <sub>3</sub>	<sup>13</sup> C	<i>ZZ</i>	21.82		36.50		44.47		170.98	
			<i>EZ(E)</i> <sup>b</sup>	20.97		33.49		48.05		170.70	
			<i>EZ(Z)</i> <sup>b</sup>	21.82		37.70		46.60		170.92	
			<i>EE</i>	21.01		33.93		48.99		170.18	
4	CDCl <sub>3</sub>	<sup>13</sup> C	<i>ZZ</i>		33.21		41.04		50.70		201.00
			<i>EZ(E)</i>		32.20		42.60		50.02		200.71
			<i>EZ(Z)</i>		33.21		41.76		53.27		201.42
			<i>EE</i>		31.97		43.0		52.1		<sup>c</sup>
5	CDCl <sub>3</sub>	<sup>1</sup> H	<i>ZZ</i>	2.05	2.60	3.10	3.32	3.67	4.20		
			<i>E<sup>o</sup>Z<sup>s</sup></i>	2.14	2.64	3.00	3.29	3.70	4.11		
			<i>E<sup>s</sup>Z<sup>o</sup></i>	2.10	2.69	3.04	3.47	3.56	3.80		
			<i>EE</i>	<sup>c</sup>	<sup>c</sup>	<sup>c</sup>	<sup>c</sup>	<sup>c</sup>	<sup>c</sup>		<sup>c</sup>
	(CD <sub>3</sub> ) <sub>2</sub> CO	<sup>1</sup> H	<i>ZZ</i>	1.96	2.53	3.07	3.32	3.62	4.15		
			<i>E<sup>o</sup>Z<sup>s</sup></i>	2.05	2.60	2.91	3.38	3.68	4.17		
			<i>E<sup>s</sup>Z<sup>o</sup></i>	2.03	2.62	3.08	3.41	3.59	3.82		
			<i>EE</i>	<sup>c</sup>	2.64	<sup>c</sup>	3.42	3.72	3.97		
	CDCl <sub>3</sub>	<sup>13</sup> C	<i>ZZ</i>	21.86	33.24	37.14	40.59	43.63	52.40	171.29	200.69
			<i>E<sup>o</sup>Z<sup>s</sup></i>	21.21	33.18	33.58	41.76	46.20	53.80	170.84	201.00
			<i>E<sup>s</sup>Z<sup>o</sup></i>	21.77	31.93	37.72	42.61	46.26	51.91	171.11	200.40
			<i>EE</i>	20.98	<sup>c</sup>	<sup>c</sup>	<sup>c</sup>	48.70	52.59	<sup>c</sup>	<sup>c</sup>
DMA <sup>d</sup>	CDCl <sub>3</sub>	<sup>13</sup> C		21.4		34.8 <sup>e</sup>				169.6	
						37.8 <sup>f</sup>					
DMTA <sup>g</sup>	CDCl <sub>3</sub>	<sup>13</sup> C			32.8		44.0 <sup>e</sup>			198.7	
							42.3 <sup>f</sup>				

<sup>a</sup>Denotes the amide and thioamide part of the molecule. <sup>b</sup>Denotes the *E* and *Z* parts of the molecule. <sup>c</sup>Signals not observed due to low intensity or overlap. <sup>d</sup>*N,N*-dimethylacetamide, data from Ref. 8. <sup>e</sup>*cis* to the C=O (C=S) group. <sup>f</sup>*trans* to the C=O (C=S) group. <sup>g</sup>*N,N*-dimethylthioacetamide, data from Ref. 8.

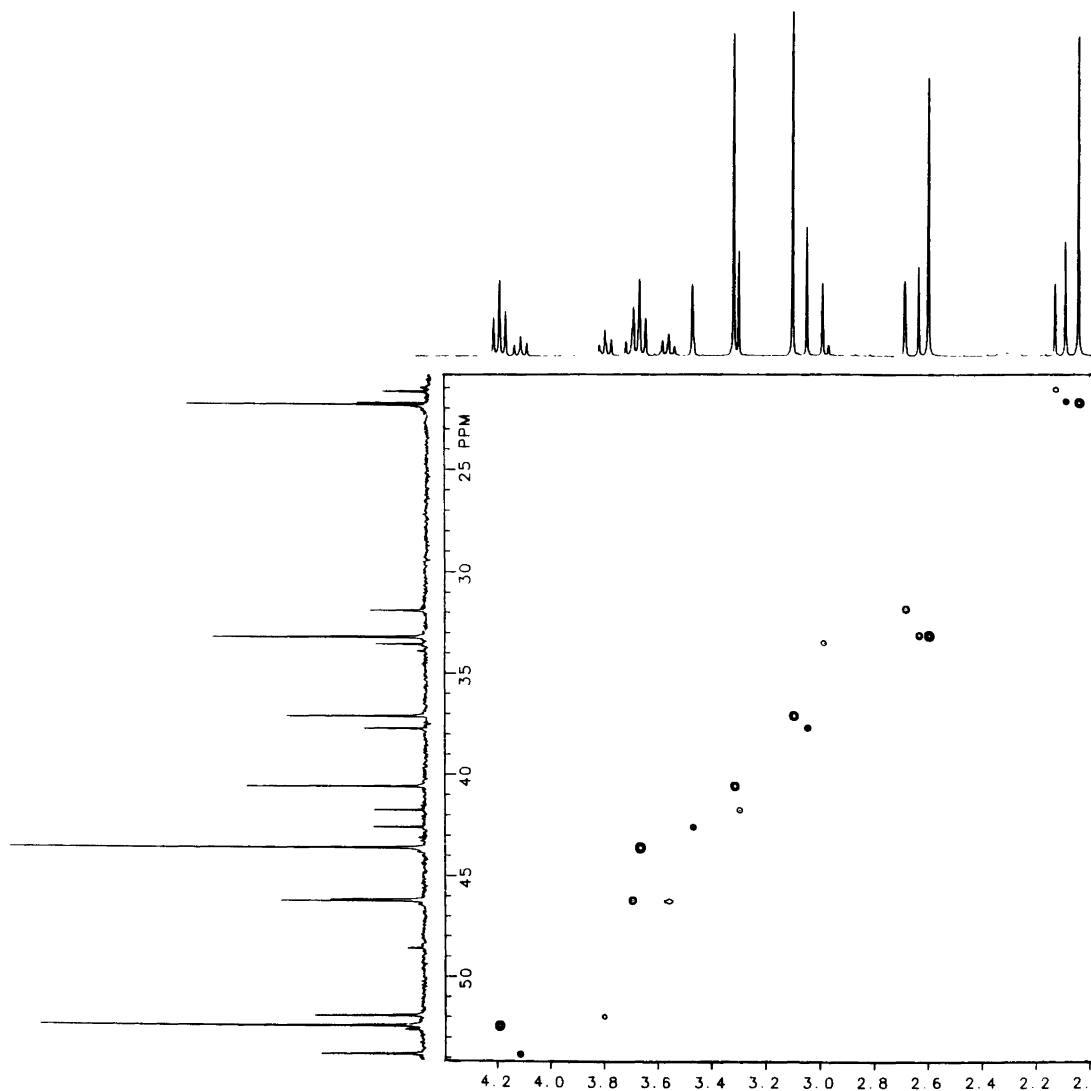


Fig. 1. 2D  $^1\text{H}$ - $^{13}\text{C}$  correlation spectrum of **5** in  $\text{CDCl}_3$ , showing the  $^1\text{H}$  and  $^{13}\text{C}$  spectra in the horizontal and vertical directions, respectively, as well as the cross peaks for the ZZ,  $E^O Z^S$  and  $E^S Z^O$  forms.

approximation, the conformational distribution on the basis of the measurable sum of the vicinal coupling constants ( $N = J + J'$ ) following the procedure of Abraham and Gatti.<sup>7</sup> The results are shown in Table 1.

For the newly synthesized "mixed" amide-thioamide **5**, the  $^1\text{H}$  NMR chemical shifts in  $\text{CDCl}_3$  and  $(\text{CD}_3)_2\text{CO}$ , as well as the  $^{13}\text{C}$  NMR chemical shifts in  $\text{CDCl}_3$ , are shown in Table 2

together with  $^{13}\text{C}$  NMR chemical shifts for the diamide **3** and the dithioamide **4**. The assignment of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR chemical shifts was assisted by comparison with the previously published data<sup>1</sup> and by consideration of signal intensities. For compound **5**, the assignment was confirmed by a two-dimensional heteronuclear NMR correlation (Fig. 1).

The MM2 calculations predict 5–6 energy min-

Table 3. Calculated minimum energies, dihedral angles and dipole moments for **1**, **3**, **4** and **5** (dielectric constant = 1.5). The lowest minima for each form are given.

Compound	Conformation	Energy/kJ mol <sup>-1</sup>	$\omega$ /deg	$\theta_1$ /deg	$\theta_2$ /deg	$\mu$ D
<b>1</b>	<i>ZZ</i>	44.1	+ 64	-85	-85	3.1
		55.6	180	-81	+82	0.0
	<i>EZ</i>	55.1	+176	-82	-83	6.5
		55.5	+179	-82	+81	4.7
	<i>EE</i>	57.8	+178	-82	-82	2.7
		57.9	180	-82	+82	0.0
<b>3</b>	<i>ZZ</i>	56.3	+ 67	-85	-85	2.3
		65.4	+179	-82	-82	0.1
	<i>EZ</i>	67.2	+179	-82	-81	6.3
		68.5	-179	-82	+79	5.5
	<i>EE</i>	69.3	180	-79	+79	0.0
		70.9	-174	-80	-79	0.9
<b>4</b>	<i>ZZ</i>	67.6	+ 74	-90	-90	3.3
		68.4	-179	-83	-83	0.1
	<i>EZ</i>	71.1	+179	-78	+82	5.7
		71.3	-178	-80	-85	6.7
	<i>EE</i>	71.5	180	-78	+77	0.0
		73.1	-175	-80	-80	1.4
<b>5</b>	<i>ZZ</i>	61.6	+ 70	-83	-91	2.9
		66.9	-179	-82	+83	0.4
	<i>E<sup>o</sup>Z<sup>s</sup></i>	70.1	-176	-82	-84	6.4
		70.2	+179	-81	+82	5.6
	<i>E<sup>s</sup>Z<sup>o</sup></i>	68.5	180	-81	-78	6.6
		69.4	-179	-82	+77	5.6
	<i>EE</i>	70.4	180	-80	+77	0.5
		72.1	-175	-81	-79	1.3

<sup>a</sup>N-CH<sub>2</sub>-CH<sub>2</sub>-N dihedral angle. <sup>b</sup>CH<sub>2</sub>-CH<sub>2</sub>-N-C(=Y) dihedral angle. In **5**,  $\theta_1$  refers to the amide and  $\theta_2$  to the thioamide part.

ima for each of the *EE*, *EZ* and *ZZ* forms for **1**, **3**, **4** and **5**. The energies and dihedral angles for the two lowest minima for each form are given in Table 3.

The results obtained for **1** and **3** differ to some extent from those obtained with the MM1 force field.<sup>1</sup> While the latter indicated a *gauche* conformer as the most stable *EE* and *EZ* form, we now find the *anti* forms to be favoured by 8–20 kJ mol<sup>-1</sup>. Only for the *ZZ* form is a *gauche* conformer found to be the most stable one (Fig. 2), its energy being 9 kJ mol<sup>-1</sup> below that of the next most stable, which is an *anti* conformer. The *ZZ*

forms are still predicted to be more stable than the *EZ* and *EE* forms, which are of similar energy.

## Discussion

The results reported in Table 1 show that in the low-polarity solvent (CDCl<sub>3</sub>) the following order of populations of the conformations with respect to the (thio)amide bond is generally observed:

$$p(ZZ) > p(ZE) > p(EE)$$

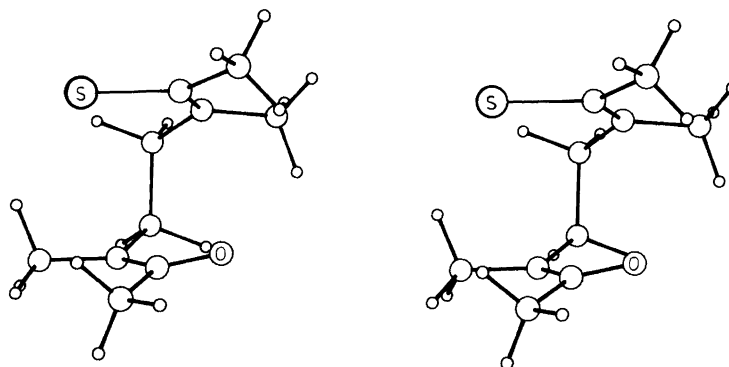


Fig. 2. Stereo-view of the calculated most stable conformer of the ZZ form of 5.

The dominance of the ZZ form is stronger for the bis-thioamides than for the corresponding diamides.

The conformational distribution (*anti-gauche*) about the ethane bond, as deduced from NMR spectra, is rather complicated and does not always correspond to general dominance of the *gauche* form as suggested on the basis of MM1 calculations for 1 and 3.<sup>1</sup> For the ZZ forms in CDCl<sub>3</sub>, the amount of the *anti* conformer increases with the size of the R group (1 → 3 → 8) as well as on replacement of O by S (3 → 5 → 4). This is probably due to R–C/C=X, R–C/R–C and C=X/C=Y repulsive interactions. In keeping with this interpretation, the MM2 calculations predict a progressive destabilization of the ZZ, *gauche* forms with respect to the *anti* form in the series 1, 3, 5, 4, the *anti-gauche* energy differences being 11, 9, 5 and 1 kJ mol<sup>-1</sup>, respectively.

In the more polar solvent (acetone-*d*<sub>6</sub>), the amounts of EZ and EE forms generally increase at the expense of the ZZ form, the conformational distribution being shifted towards the statistical distribution. On the other hand, the ZZ, *gauche* form is stabilized relative to the ZZ, *anti* form by increased solvent polarity for 4, 5 and especially 8, but not for 3. For the EZ forms, the *anti-gauche* equilibrium does not seem to be seriously affected by the solvent.

Solvent polarity may affect the conformational equilibria in several ways. According to the MM2 calculations, the ZZ, *gauche* forms are stabilized by dipole-dipole attractions of ca. 3 kJ mol<sup>-1</sup>. As shown in Ref. 1, these diminish with increasing dielectric constant of the medium. On the other

hand, the ZZ, *gauche* form and the EZ, *anti* forms have higher dipole moments than the ZZ, *anti* and EE, *anti* forms, and should be more stabilized by polar solvents. However, individual solvation of the thioamide groups, especially in the *anti* forms, and quadrupolar solute-solvent interactions may also play a role and perhaps explain the increasing population of EE forms with increasing solvent polarity.

It may seem futile to search for some stereochemical dependence of the <sup>13</sup>C chemical shifts, considering the complexity of the conformational equilibria. However, it seems as if the <sup>13</sup>C chemical shifts are more sensitive to conformational changes about the (thio)amide bond than about the CH<sub>2</sub>–CH<sub>2</sub> bond. Thus, the δ<sub>C</sub> values (Table 2) for the CH<sub>3</sub>–C and CH<sub>3</sub>N methyl carbons in 3 as well as in the amide part in 5 are close (within ± 1.5 ppm) to those measured for *N,N*-dimethylacetamide (DMA in Table 2), and the same is true for the resonances of the thioamide groups in 4 and 5 with respect to those of *N,N*-dimethylthioacetamide (DMTA in Table 2).<sup>8</sup> The tendency of the CH<sub>3</sub>N and CH<sub>2</sub>N carbons to resonate at higher field (up to 3–4 ppm) when *cis*-oriented than when *trans*-oriented with respect to the oxygen atom was also generally observed in our systems. The opposite trend, somewhat weaker (1–2 ppm), was observed for the dithioamide 4 and for the thioamide part of 5, and is also seen for dimethylthioacetamide.<sup>8</sup>

**Conclusion.** The analysis of the NMR spectra shows that except for the formyl derivative (1), the dominance of the ZZ forms is not exclusively

or even predominantly due to a large stabilization of the *gauche* conformation. MM2 calculations suggest that the *ZZ*, *gauche* forms are stabilized by dipole-dipole interactions, but that non-bonded interactions play the most important role in determining the conformational equilibria. The latter prediction is clearly corroborated by the experimental results.

Increasing solvent polarity increases the proportion of *EZ* and *EE* forms at the expense of the *ZZ* forms, but the effects on the *anti-gauche* equilibria are less clear-cut.

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