

Conformational Analysis of *N,N'*-Dimethyl-*N,N'*-diacyl-1,2-diaminoethanes and -1,3-diaminopropanes and Their Thio Analogues. A ^1H NMR and Molecular Mechanics Study Including Dipole-dipole Interactions

SÖREN KARLSSON, TOMMY LILJEFORS and JAN SANDSTRÖM *

Division of Organic Chemistry 1, Chemical Center, University of Lund, P.O.B. 740, S-220 07 Lund 7, Sweden

The signals due to the *Z-Z*, *E-Z* and *E-E* forms of ten representative title compounds have been identified in the ^1H NMR spectra by solvent effects and coupling constants. In general, the *Z-Z* form shows a much stronger preponderance than expected on purely statistical grounds. For two simple *N,N'*-ethylenebisamides this is shown by molecular mechanics calculations to be due to a combination of steric and dipole interaction effects, leading to a general stabilization of the *gauche* relative to the *trans* form and to a stability order $Z-Z > E-Z > E-E$.

When studying the NMR spectra of some *N,N'*-dialkyl-*N,N'*-diacylethylenediamines, Siddall¹ observed that the *N*-alkyl proton shifts of the *Z* parts were different in the *Z-Z* and *E-Z* conformers, and similarly for the *E* parts in the *E-E* and *E-Z* forms. Since such differences are unlikely in the staggered *trans* conformation (Fig. 1a), he proposed an intramolecular association between the two amide groups, which should place them in closer proximity.

The investigation described here was initiated by the observation that the NMR spectrum of *N,N'*-dimethyl-*N,N'*-bis(phenylthioacetyl)-ethylenediamine (δ) did not show the expected nearly statistical population ratio of 1:2:1 between the *E-E*, *E-Z*, and *Z-Z* conformers, but that the population ratio of the three conformers was about 1:3:6 in deuteriochloroform solution. In *N*-methyl-*N*-ethylthioacetamide the *E* and *Z* rotamers have nearly equal popula-

tions in CDCl_3 and C_6D_6 solutions,² and similar relations are expected for δ in the absence of a specific interaction between the thioamide groups, *i.e.* the *E-E*, *E-Z*, and *Z-Z* conformer ratio should be close to 1:2:1.

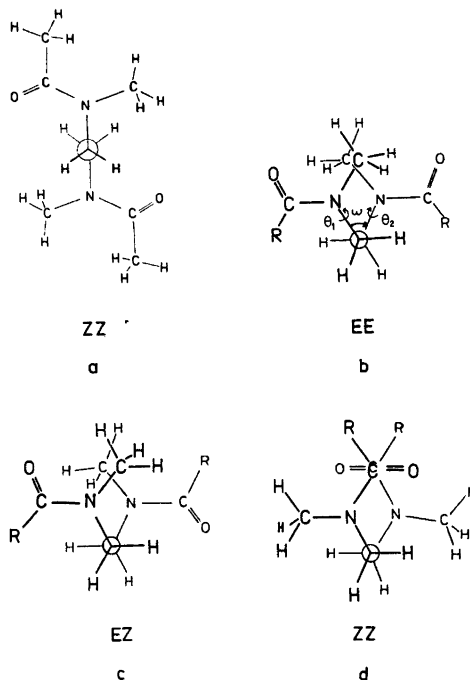
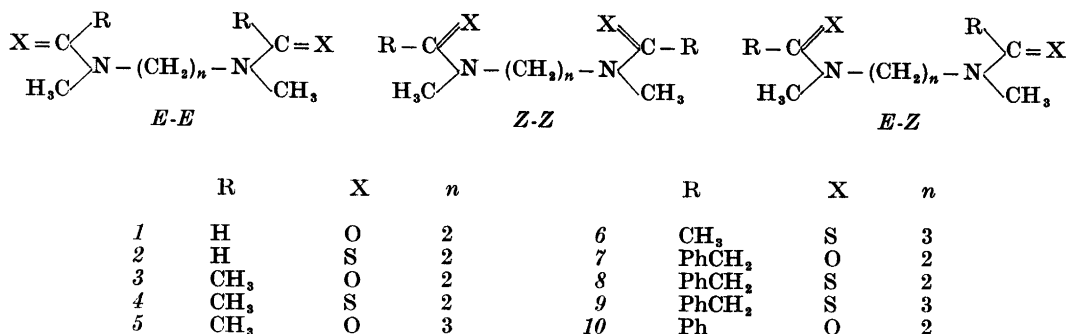


Fig. 1. The *trans* *Z-Z* conformation (a) and minimum energy conformations for the *E-E* (b), *E-Z* (c) and *Z-Z* (d) forms.

* Author to whom inquiries should be addressed.



Scheme 1.

In order to identify the rotamers and to try to rationalize the observed conformer distribution, a number of analogous amides and thioamides derived from *N,N'*-dimethylethylenediamine and *N,N'*-dimethylpropane-1,3-diamine (Scheme 1) have been prepared for an NMR study. Compounds 1 and 3 have been subjected to molecular mechanics calculations in order to find the minimum energy conformations and their energy differences and also to find the interactions responsible for the stabilization of the preferred conformations.

Diamides of the types studied here have been of interest as models for polyamides. Thus 3 and 10 were found to give rotamer ratios deviating rather much from the statistical one in phenol-water solution,³ but this observation was only rationalized with reference to the rotamer ratio in methyl *N*-acetylsarcosinate.⁴ For the latter compound, the assignment of NMR resonances is questionable, being based only on analogy with *N,N*-dimethylformamide. The same compounds have been studied in benzene solution, where a *Z-Z* to *E-Z* ratio of near unity was observed, but no *E-E* form was reported.⁵ Compound 3 has also been studied by the LIS technique,⁶ but the assignments for the uncomplexed diamide are at variance with those reached in the present study.

EXPERIMENTAL

Preparative part. *N,N'*-Dimethyl-*N,N'*-diformylethylenediamine (1) was prepared by refluxing *N,N'*-dimethylethylenediamine with an excess of ethyl formate for 4 h, followed by

evaporation, recrystallization from benzene and vacuum sublimation. Colourless prisms in 76 % yield, m.p. 80–82 °C (lit.⁷ 81–82 °C).

N,N'-Dimethyl-*N,N'*-bis(thioformyl)ethylenediamine (2) was prepared by refluxing 1 with excess P₄S₁₀ in toluene for 2 h with stirring, followed by evaporation of the toluene solution and recrystallization of the residue from ethanol. Colourless prisms in 14 % yield, m.p. 135–140 °C. Found: C 40.7; H 6.76; N 15.5; S 35.9. Calc. for C₆H₁₂N₂S₂: C 40.9; H 6.86; N 15.9; S 36.4.

N,N'-Dimethyl-*N,N'*-diacetyethylenediamine (3) was obtained on reaction of *N,N'*-dimethylethylenediamine with excess acetic anhydride followed by fractional distillation. The product, b.p. 1 mmHg, 125–133 °C, crystallized from light petroleum (b.p. 80–100 °C) in 89 % yield as colourless prisms, m.p. 92.5–94 °C (lit. 90–92 °C,⁸ 94.5–95 °C³). Anal. C₈H₁₆N₂O₂: C, H, N, O.

N,N'-Dimethyl-*N,N'*-bis(thioacetyl)ethylenediamine (4) was prepared essentially as 2 with 3 as starting material, but dioxane was used as solvent and the crude product was purified by extraction with chloroform, evaporation and crystallization of the residue first from toluene–light petroleum and then from toluene to give a 35 % yield of colourless prisms, m.p. 129–131 °C. Anal. C₈H₁₆N₂S₂: C, H, N, S.

N,N'-Dimethyl-*N,N'*-diacetylpropane-1,3-diamine (5) was prepared essentially as 3 starting from *N,N'*-dimethylpropane-1,3-diamine. The product was obtained as hygroscopic prisms, m.p. 63 °C, b.p. 2 mmHg, 190–194 °C, *n*_D²⁰ 1.4845, in 61 % yield. Found: C 57.5; H 9.68; N 14.8; O 17.9. Calc. for C₉H₁₈N₂O₂: C 58.0; H 9.74; N 15.0; O 17.2.

N,N'-Dimethyl-*N,N'*-bis(thioacetyl)propane-1,3-diamine (6) was obtained as 4, starting from 5, in 20 % yield as colourless prisms, m.p. 128–130 °C. Anal. C₉H₁₈N₂S₂: C, H, N, S.

N,N'-Dimethyl-*N,N'*-bis(phenylacetyl)ethylenediamine (7) was prepared by Schotten-Baumann acylation of *N,N'*-dimethylethylenediamine with phenylacetyl chloride. The product could only be induced to crystallize after

column chromatography on activated silica. 2-Butanone eluted impurities, and 7 was eluted by a 1:1 (v/v) mixture of acetone and 2-butanone. It was obtained as colourless prisms, m.p. 79.5–82.5°C, in 44% yield after two recrystallizations from cyclohexane and one from toluene. Anal. C₂₀H₂₄N₂O₂: C, H, N, O.

N,N'-Dimethyl-N,N'-bis(phenylthioacetyl)-ethylenediamine (8) was prepared by reaction between methyl phenyldithioacetate* and N,N'-dimethylethylenediamine in the molar proportion 2:1 without solvent. The product was recrystallized four times from toluene to give a 60% yield of colourless prisms, m.p. 145–148°C. Anal. C₂₆H₂₄N₂S₂: C, H, N, S.

N,N'-Dimethyl-N,N'-bis(phenylthioacetyl)-propane-1,3-diamine (9) was prepared as 8. Colourless prisms, m.p. 92–96°C, were obtained in 25% yield after two recrystallizations from toluene–light petroleum and two from toluene. Anal. C₂₁H₂₈N₂S₂: C, H, N, S.

N,N'-Dimethyl-N,N'-dibenzoylethylenediamine (10) was prepared by reaction of N,N'-dimethylethylenediamine with benzoyl chloride in dichloromethane in the presence of triethylamine. After 24 h the separated solid was triturated with hot water and recrystallized from ethanol to give a 66% yield of colourless prisms, m.p. 174–175.5°C (lit.¹⁰ 177–178°C). Anal. C₁₈H₂₀N₂O₂: C, H, N, O.

NMR measurements. These were performed with a JEOL model MH-100 NMR spectrometer, operating in the field sweep, synchro-track mode with the internal lock on TMS. The chemical shifts were read with a frequency counter, which measures the frequency difference between the lock signal and the observing frequency.

The populations of the observed conformers were determined by fitting calculated Lorentzians to the experimental N-methyl signals, taking coupling effects into account when appropriate.

The ASIS study was performed by measuring the spectra of compounds 1–10 as 0.1 M solutions in deuteriochloroform and in *o*-dichlorobenzene (ODC) and also in 3:1, 1:1, and 1:3 mixtures (v/v) of these solvents. To avoid exchange broadening, compound 3 was studied at +25°C, 5 at –6°C, and 10 at +6°C, whereas all other compounds were studied at ambient temperature (+35°C).

The ASIS plots were constructed by the method of least squares, based on eqn. (1), where

$$\nu_x = aP(\text{CDCl}_3) + b \quad (1)$$

ν_x is the frequency of the signal under study and $P(\text{CDCl}_3)$ is the volume percentage of this solvent. The ASIS are given by a in Table 3.

Molecular mechanics calculations. Geometries and conformational energies were calculated using Allinger's molecular mechanics method.^{11,12} The 1973 force field¹² was employed in the

Table 1. Force field parameters.^a

| | | |
|--|-------------------------------|--------------------------------|
| van der Waals constants | | |
| $E_v = -2.25\epsilon(r^*/r)^6 + 8.28 \times 10^5 \epsilon \exp(-r/0.0736r^*)$ | | |
| Atom | $r^*/\text{\AA}$ | $\epsilon/\text{kJ mol}^{-1}$ |
| O | 1.650 | 0.192 |
| N | 1.700 | 0.163 |
| Stretching constants | | |
| $E_s = 301.0k_s(l-l_0)^2 [1 + C_s(l-l_0)]$ $C_s = -2.00$ | | |
| Bond | $j_0/\text{\AA}$ | $k_s/\text{mdyn \AA}^{-1}$ |
| C=O | 1.215 | 10.80 |
| C _{CO} -N(<i>sp</i> ²) | 1.367 | 5.00 |
| C(<i>sp</i> ³)-N(<i>sp</i> ²) | 1.449 | 3.40 |
| Bending constants | | |
| $E_b = 0.091688k_b(\theta-\theta_0)^2 [1 + C_f(\theta-\theta_0)]$ | | |
| $C_f = -0.006$ | | |
| Angle | $\theta_0/\text{deg.}$ | $k_b/\text{mdyn \AA rad}^{-2}$ |
| H-C=O | 120.6 | 0.25 |
| C-C=O | 122.8 | 0.57 |
| N-C=O | 124.0 | 0.50 |
| H-C _{CO} -N | 110.0 | 0.40 |
| C-C _{CO} -N | 112.7 | 0.40 |
| C-N-C _{CO} | 121.0 | 0.70 |
| C-N-C | 115.0 | 0.50 |
| H-C-N | 109.5 | 0.42 |
| C-C-N | 109.5 | 0.42 |
| Out-of-plane N(<i>sp</i> ²) | 0.0 | 0.05 |
| Out of plane C _{CO} | 0.0 | 0.80 |
| Stretch-bend constants | | |
| $E_{sb} = 10.50703k_{sb}(\theta-\theta_0)(l_1-l_0) + (l_2-l_0)$ | | |
| Atoms | $k_{sb}/\text{mdyn rad}^{-1}$ | |
| X-F-Y | 0.120 | |
| X-F-H | 0.040 | |
| F, X, Y are C, N or O | | |
| Torsional constants | | |
| $E_t = V_1/2(1 + \cos \omega) + V_2/2(1 - \cos 2\omega) + V_3/2(1 + \cos 3\omega)$ | | |
| Angle | V_2 | $V_3/\text{kJ mol}^{-1}$ |
| H-C-C-N | | 2.22 |
| N-C-C-N | | 2.22 |
| X-C-N-Y | | 4.18 |
| X-C _{CO} -N-C | 25.1 | |
| O=C-N-C | 16.7 | |
| H-C-C _{CO} -N | | 0.0 |
| H-C-C=O | | -3.1 |
| X=H or C(<i>sp</i> ³); Y=C _{CO} or C(<i>sp</i> ²) | | |
| Bond moments | | |
| | μ/D | |
| C=O | 2.91 | |
| C _{CO} -N | -1.16 | |

^a C-H parameters are taken from Ref. 12.

Table 2. ¹H Chemical shifts ^a of the different conformers of compounds 1–10.

| Compound No. | R | X | n | N-CH ₃ | | | N-CH ₃ | | | R | | |
|----------------|-------------------|---|---|-------------------|-------------------|--------|-------------------|--------|--------|------|----------------|--------|
| | | | | E-E | E-Z(E) | E-Z(Z) | E-E | E-Z(E) | E-Z(Z) | E-E | E-Z(E) | E-Z(Z) |
| 1 | H | O | 2 | 3.40 | 3.46 ^b | 3.55 | 2.90 | 2.92 | 2.94 | 3.00 | — ^c | — |
| 2 ^d | H | S | 2 | 3.29 | 3.59 ^b | 3.86 | 2.95 | 3.07 | 2.81 | 3.00 | — ^c | — |
| 3 | CH ₃ | O | 2 | 3.46 | 3.47 ^b | 3.52 | — ^e | 2.95 | 3.03 | 3.03 | 2.00 | 2.10 |
| 4 | CH ₃ | S | 2 | 3.81 | 4.09 ^b | 4.32 | 3.45 | 3.49 | 3.26 | 3.35 | 2.67 | 2.63 |
| 5 | CH ₃ | O | 3 | — ^e | 3.44 | 3.29 | 2.94 | 2.92 | 3.02 | 3.01 | 2.18 | 2.10 |
| 6 | CH ₃ | S | 3 | — ^e | 3.66 | 3.95 | 3.45 | 3.45 | 3.28 | 3.28 | 2.69 | 2.62 |
| 7 | PhCH ₂ | O | 2 | — ^e | 3.66 | 3.54 | — ^e | 2.94 | 2.91 | 3.00 | — ^e | 3.66 |
| 8 | PhCH ₂ | S | 2 | — ^e | 3.87 ^b | 4.23 | — ^e | 3.45 | 2.97 | 3.20 | — ^e | 4.30 |
| 9 | PhCH ₂ | S | 3 | — ^e | 3.55 | 3.76 | 3.19 | 3.40 | 2.93 | 3.16 | — ^e | 4.22 |
| 10 | Ph | O | 2 | 3.39 | 3.62 ^b | 3.93 | 2.77 | 3.24 | 2.73 | 3.11 | — | 4.27 |

^a In ppm downfield from TMS. Solvent CDCl₃, unless stated otherwise. ^b Centre of A₂B₂ multiplet. ^c Not identified due to overlap. ^d In ODC for solubility reasons. ^e Not observed.

calculations of interactions involving only carbon and hydrogen. Parameters describing the amide skeleton were taken from earlier work¹³ (carbonyl group parameters) or obtained by fitting to electron diffraction geometries of simple amides.^{14–16} The amide skeleton force field is summarized in Table 1.

A problem in the parametrization is the choice of intrinsic torsional terms describing the variation in energy for rotation around the N(sp²)–C(sp³) and C(sp²)–C(sp²) bonds. The three-fold torsional terms chosen (Table 1) give 4.69 and 6.11 kJ/mol, respectively, for the barrier to rotation around these bonds in *N*-methylacetamide. In the calculated lowest energy conformation one C–H bond in the methyl group attached to the carbonyl group eclipses this group. The *N*-methyl group is staggered with respect to the C–N amide bond, in agreement with the electron diffraction structure.¹⁵ There are no experimental data on the rotation barrier for the carbonyl-methyl group in amides but the barrier height has been estimated to be ca. 4 kJ/mol.^{14,17} The only experimental value for the *N*-methyl rotational barrier comes from a recent measurement of ¹³C relaxation times (*T*₁) in *N,N*-dimethylformamide.¹⁸ From rate constants at –57.6 °C, Δ*G*‡ = 7.5–8.4 kJ/mol can be calculated. Since the uncertainties in these values are rather large, we have not made any attempt to reproduce them. In earlier work on amides and peptides *V*₃ terms for the *N*-methyl torsion varying from 2.1–6.3 kJ/mol have been used.¹⁹ The twofold torsional terms for the C–N amide bond given in Table 1 were chosen to give a calculated barrier to rotation around this bond of ca. 82 kJ/mol.²⁰ The numbers used are only rough estimates since they are of minor importance in this work, where deviations from planarity of the amide skeleton are insignificant.

Dipole interaction energies were calculated from the expression (2).²¹

$$E_{\text{DIP}} = K\mu_A\mu_B (\cos X - 3 \cos \alpha_A \cos \alpha_B) / R^3 D \quad (2)$$

where μ_A and μ_B are bond moments, R is the distance between the midpoints of the bond dipoles and X , α_A and α_B are angles describing their relative orientation. D is the dielectric constant and K is an energy conversion factor.

The bond moments used for the C=O and C–N dipoles (Table 1) reproduce the experimental magnitude (3.71 *D*)²² and orientation (39.6° with respect to the N–C bond)²² of the dipole moment in formamide.

RESULTS

The ¹H NMR spectral assignments of two representative compounds (1 and 4) are discussed in detail below, and data for the

Table 3. Aromatic solvent induced shifts ^a for the different conformers of compounds 1 and 3–10.

| Compound No. | N-CH ₂ | | | | N-CH ₃ | | | | R | | | |
|--------------|-------------------|---------------|---------------|------------|-------------------|---------------|---------------|------------|------------|---------------|---------------|------------|
| | <i>E-E</i> | <i>E-Z(E)</i> | <i>E-Z(Z)</i> | <i>Z-Z</i> | <i>E-E</i> | <i>E-Z(E)</i> | <i>E-Z(Z)</i> | <i>Z-Z</i> | <i>E-E</i> | <i>E-Z(E)</i> | <i>E-Z(Z)</i> | <i>Z-Z</i> |
| 1 | 0.36 | — | — | 0.22 | 0.24 | 0.16 | 0.38 | 0.29 | — | — | — | — |
| 3 | 0.30 | — | — | 0.14 | — | 0.13 | 0.31 | 0.25 | — | 0.10 | 0.23 | 0.17 |
| 4 | 0.31 | — | — | 0.13 | 0.21 | 0.15 | 0.35 | 0.30 | 0.20 | 0.09 | 0.24 | 0.20 |
| 5 | — | 0.20 | 0.17 | 0.20 | 0.18 | 0.17 | 0.36 | 0.32 | 0.26 | 0.22 | 0.21 | 0.21 |
| 6 | — | 0.30 | 0.18 | 0.17 | 0.20 | 0.16 | 0.37 | 0.36 | 0.21 | 0.15 | 0.19 | 0.19 |
| 7 | — | — | — | 0.12 | — | 0.12 | 0.20 | 0.21 | — | 0.02 | 0.13 | 0.13 |
| 8 | — | — | — | 0.13 | — | 0.14 | 0.27 | 0.25 | — | 0.01 | 0.15 | 0.13 |
| 9 | — | 0.19 | 0.19 | 0.13 | 0.15 | 0.14 | 0.24 | 0.29 | — | 0.05 | 0.10 | 0.10 |
| 10 | 0.19 | — | — | 0.17 | 0.22 | 0.07 | 0.28 | 0.17 | — | — | — | — |

^a *a* in eqn. 1.

remaining compounds are collected in Tables 2 and 3.

N,N'-Dimethyl-*N,N'*-diformylethylenediamine (1) in deuteriochloroform solution shows four narrow doublets in the *N*-methyl region, *A* (δ 2.90, *J* 0.5 Hz, *p** 0.10), *B* (δ 2.92, *J* 0.5 Hz, *p* 0.22), *C* (δ 2.94, *J* 0.3 Hz, *p* 0.22) and *D* (δ 3.00, *J* 0.3 Hz, *p* 0.46). The ethylene part consists of two singlets, *E* (δ 3.40, *p* 0.10) and *F* (δ 3.54, *p* 0.46) and an A₂B₂ spectrum centered at δ 3.45 (*p* 2 × 0.22). The formyl proton region is not well resolved, and no assignments have been made here.

By assignment of the *N*-methyl signals in *N,N*-dimethylformamide using the NOE method, Anet and Bourn²³ have demonstrated that the formyl proton is more strongly coupled to the *Z* than to the *E* methyl proton. Hatton and Richards²⁴ have shown that the *E* methyl signal in *N,N*-dimethylamides is shifted more rapidly upfield on dilution with an aromatic solvent than the *Z* methyl signal, and this effect is ascribed to a time-average localization of the solvating aromatic molecules away from the negative end of the amide electric dipole (ASIS),^{15,26} The ASIS values for signals *A* to *F* are 0.24, 0.16, 0.38, 0.29, 0.36 and 0.22, respectively, and $\Delta\nu_{AB}$ in the A₂B₂ spectrum is strongly increased with increasing ODC concentration.

The *A* and *B* signals are assigned to methyl protons in *E* forms** by their larger couplings

to the formyl proton and by their small ASIS values, and the populations together with the ASIS values for the methylene proton signals unequivocally assign *A* to the *E-E* form, *B* to the *E* part and *C* to the *Z* part in the *E-Z* form, and *D* to the *Z-Z* form. Signal *E* is assigned to the CH₂ protons in the *E-E* form and *F* to the same protons in the *Z-Z* form. Thus the *E-E*:*E-Z*:*Z-Z* ratio for this compound in deuteriochloroform is 0.10:0.44:0.46, which shows a smaller deviation from the statistical distribution than most of the other molecules.

N,N'-Dimethyl-*N,N'*-bis(thioacetyl)ethylenediamine (4). The spectrum of this compound in ODC is shown in Fig. 2. Signals *D* and *H* appear as quartets (*J* = 0.5 Hz) in expanded spectra, and either of them changes into a sharp singlet on selective irradiation of the other one.

With increasing temperature, all signals broaden, and above 150 °C *A* to *C* merge into one (N-CH₂), *D* to *G* into another (N-CH₃) and *H* to *K* into a third one (C-CH₃). The ASIS values for signals *A* and *C* to *G* are 0.13, 0.31, 0.15, 0.21, 0.30 and 0.35. These data together with the signal intensities clearly assign *A*, *F* and *J* to the *Z-Z* form, *D* and *H* to the *E* part and *G* and *K* to the *Z* part of the *E-Z* form, and the small signals *C*, *E* and *I* to the *E-E* form. The *B* multiplet is ascribed to the methylene protons of the *E-Z* form. The assignment of *D* and *H* to a *trans* methyl pair and *G* and *J* to a *cis* pair is further strengthened by the coupling, which is larger in the former case. Thus ⁵*J*_{H-H,trans} in *N,N*-dimethylthioacetamide is 0.7 Hz and ⁵*J*_{H-H,cis} is 0 Hz.²⁷

* *p* stands for fractional population.

** Note that the *N*-methyl group is *Z* to the carbonyl group in the *E* form.

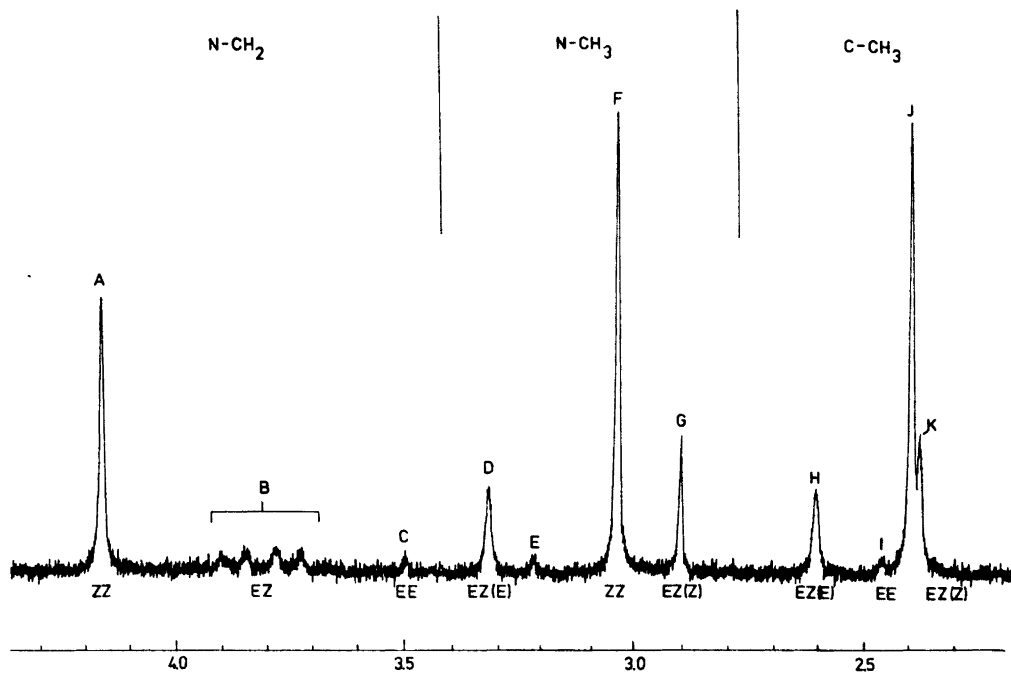


Fig. 2. ^1H NMR spectrum of **4** in ODC.

The $E-E : E-Z : Z-Z$ ratio in this compound in deuteriochloroform solution is thus 0.02:0.30:0.68, *i.e.* it deviates more from the statistical distribution than in **1**.

DISCUSSION

The preponderance of the $Z-Z$ over the other forms was first ascribed to a dipole-dipole attraction in a *gauche* conformation, since only in the $Z-Z$ form could the amide/thioamide electric dipoles attain a favourable antiparallel arrangement (Fig. 1d). In the molecular mechanics calculations performed on compounds **1** and **3**, the minimum energy conformations were found by allowing the molecule to relax from all conceivable *gauche* and *anti* conformations. The dielectric constant D in expression (2) cannot be given the value appropriate for the bulk solvent. Rather it should be a composite of this constant and the (unknown) effective constant of the substrate. For the latter, some guidance may be obtained from the value of $D=4$, which Momany *et al.*²⁸ recommend for a polypeptide crystal. We have performed the calculations with three values for D (1.0,

4.0 and 8.0). The value for ODC is 9.93 and for deuteriochloroform 4.70.

The lowest-energy $E-E$, $E-Z$, and $Z-Z$ conformations are shown in Fig. 1, and data for all energy minima are found in Table 5. The

Table 4. Populations of the different conformers.

| Compound | Solvent | Ratio | | |
|-----------|-------------------|----------------|-------|-------|
| | | $E-E$ | $E-Z$ | $Z-Z$ |
| 1 | CDCl_3 | 0.10 | 0.44 | 0.46 |
| 1 | ODC | 0.17 | 0.46 | 0.37 |
| 2 | ODC | 0.05 | 0.59 | 0.36 |
| 3 | ODC | 0.08 | 0.40 | 0.52 |
| 4 | CDCl_3 | 0.02 | 0.30 | 0.68 |
| 4 | ODC | 0.05 | 0.44 | 0.51 |
| 4 | $\text{DMSO}-d_6$ | 0.16 | 0.48 | 0.36 |
| 5 | CDCl_3 | 0.09 | 0.55 | 0.36 |
| 6 | CDCl_3 | 0.10 | 0.48 | 0.42 |
| 7 | CDCl_3 | — ^a | 0.43 | 0.57 |
| 8 | CDCl_3 | 0.10 | 0.29 | 0.61 |
| 9 | CDCl_3 | 0.12 | 0.42 | 0.46 |
| 10 | CDCl_3 | 0.08 | 0.18 | 0.74 |

^a Not observed, possibly due to overlap in all solvents.

Table 5. Calculated minimum energy conformations.^a

| | $\omega^{\circ b}$ | $\theta_1^{\circ c}$ | $\theta_2^{\circ c}$ | μD | Energy/ kJ mol ⁻¹ |
|----------------------|--------------------|----------------------|----------------------|---------|---------------------------------|
| Compound 1 | | | | | |
| <i>E-E</i> | 61 | 81 | 80 | 4.6 | 47.4 |
| <i>E-Z</i> | 57 | 83 | 75 | 2.4 | 44.0 |
| <i>Z-Z</i> | -63 | 84 | 84 | 3.0 | 20.0 |
| Compound 3 | | | | | |
| <i>E-E</i> (Fig. 1b) | 62 | 90 | 90 | 5.2 | 56.9 |
| <i>E-Z</i> (Fig. 1c) | 57 | 91 | 78 | 2.9 | 49.1 |
| <i>Z-Z</i> (Fig. 1d) | -64 | 86 | 86 | 2.2 | 20.0 |

^a Data for $D=1$. ^b Dihedral angle of ethane bond. ^c Dihedral angle of N-CH₂ bond. The angle is zero when the N-C(=O) bond eclipses the ethane bond.

dependence of the energies of the most stable conformer on the dielectric constant is shown in Fig. 3. Three conformations with rather close-lying energies (within 1.2 kJ/mol) are found for the *E-Z* forms of both 1 and 3, and the entropies of mixing at 307 K are included in the calculated energies. The importance of the value of the dielectric constant in empirical strain energy calculations on polar molecules has been demonstrated by Kumbar and Sankar.²⁹ These authors propose values in the range of 20 to 30 as a suitable compromise between the dielectric constants of the substrates (tryptamine and serotonin) and of water

($D=78.5$) to give agreement between calculated and experimental conformations.

Inspection of Figs. 1 and 3 and Table 5 clearly shows that the *Z-Z* conformer has the lowest energy, and that it is relatively more stabilized in 3 than in 1, all in agreement with the experimental results. It is evident that the anticipated dipole-dipole attraction in the *gauche Z-Z* form is of importance, though it decreases strongly with increasing dielectric constant (see, e.g., 4, Table 4).

The *gauche* form, however, is favoured not only by the dipole-dipole effect but also by a steric effect. The *trans* form has the higher steric energy for all arrangements of the amide groups, mainly due to interactions between the N-CH₂ group in one half of the molecule and the *N*-methyl and acyl groups in the other. The difference in steric strain between the *Z-Z* form and the other forms is less in 1 than in 3, which may explain the observed population ratios. In particular, the *E-E* form in 1 is less disfavoured by steric effects than in 3, which is also reflected in its relatively high population in the former compound.

It must be pointed out, however, that these calculations are rather approximate, partly because of the uncertainty in the effective dielectric constant and partly because it has not been possible to take the solvation energy into account. This latter contribution may, e.g., be responsible for the discrepancy between

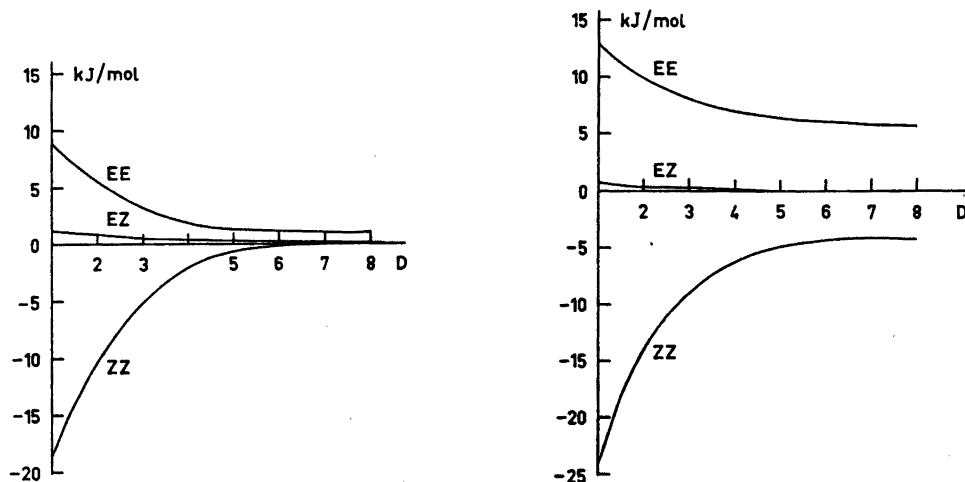


Fig. 3. Calculated minimum energy versus effective dielectric constant for 1 (a) and 3 (b).

the calculated differences in energy between the *Z-Z* form and the other forms of **3** on the one hand and the observed populations on the other hand. The calculated *Z-Z* : *E-Z* : *E-E* ratio at 305 K is 0.96:0.04:0 for *D*=4 and 0.86:0.12:0.02 for *D*=8. The experimental ratio in ODC is 0.52:0.40:0.08. In the *Z-Z* form (Fig. 1d) the *C*- and *N*-methyl groups in one amide part screen the carbonyl group in the other, thus hindering its solvation. In the low-energy *E-Z* and *E-E* forms, and in all forms of **1**, the carbonyl groups are less hindered.

The exchange between these three forms can only occur by rotation around the (thio)acyl-nitrogen bond, and it is therefore hindered by normal (thio)amide rotational barriers. By dissolving **4** and **8** and recording the NMR spectra in deuteriochloroform at low temperature, it has been possible to show that these compounds crystallize exclusively in the *Z-Z* form, and by monitoring the appearance of the *E-Z* form at -7°C , it was shown that the free energy barrier to the *Z-Z* to *E-Z* exchange in **8** is 87.9 kJ/mol, in good agreement with the value of 90.4 kJ/mol found for *N,N*-dimethylthioacetamide in ODC.³⁰

The conformer populations in the diamino-propane derivatives **5**, **6** and **9** follow a similar pattern. These compounds have a greater flexibility and have not been analyzed in detail. However, it is evident from models that when the propane chain has an energetically acceptable *gauche* (+)-*gauche* (-) conformation, the (thio)amide groups are only slightly more distant than in the *gauche* forms of the diaminoethane derivatives and in suitable positions to interact in similar ways as in these.

To conclude, we find that the intramolecular association suggested by Siddall¹ is really working. The association is caused by a combination of dipole attraction effects and steric effects and it leads to a stabilization of the *Z-Z* form and a destabilization of the *E-E* form relative to the *E-Z* form. The steric part of these effects increases with increasing size of the (thio)acyl group, and the dipole part decreases with increasing polarity of the solvent.

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