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Stereochemical Studies of 1,2-Di(thio)acetamidocyclohexanes and their *N,N'*-Dimethyl Derivatives by NMR and CD Spectroscopy and by Molecular Mechanics Calculations

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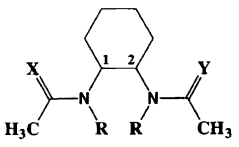
The configurations and conformations of *cis*- and *trans*- 1,2-di(thio)acetamidocyclohexane and their *N,N'*-dimethyl derivatives have been studied by ^{1}H and ^{13}C NMR spectroscopy, using chemical shifts and coupling constants, difference NOE ^{1}H NMR spectra and 2D ^{1}H–^{13}C NMR correlation spectra. For the *trans* compounds, the *Z,Z* configuration of the (thio)amide groups with equatorial (thio)acetamido groups was found to be strongly preferred. For the *cis* compounds, *E,Z* configurations of the (thio)amide groups with axial *E* and equatorial *Z* groups were found to be preferred. Empirical force-field calculations with the MM2(91) force field led to predictions for the most stable configurations and conformations, mostly in very good agreement with those obtained by NMR spectroscopy.

CD spectra recorded for the *trans*-(*R,R*)-*N*-methyl compounds in acetonitrile solution agreed well with those calculated on the basis of geometries from force-field calculations. The CD spectra calculated for the *trans*-(*R,R*)-NH- compounds and for the *cis*-monothio compounds showed poor agreement with the experimental spectra.

Previous studies[1–3] of the configuration and conformation of vicinal diacetamido compounds and their thio analogues have been concentrated on compounds in which these substituents are located on an acyclic (substituted ethane-type) moiety. It has been shown that in all cases the (thio)amide groups prefer the *ZZ* arrangement to various extents. Owing to their lack of symmetry the monothio compounds have proved to be of particular usefulness for CD studies (both diastereoisomers being chiral), as well as for NMR studies (all of the carbons and most of the protons being non-equivalent).

In the present study, the vicinal di(thio)acetamido system was introduced into a cyclohexane ring. It was expected that this conformationally more restricted system will exhibit some differences from the open-chain compounds and will prove more suitable for ^{1}H NOE studies. It was also considered of interest to compare the conformational energies of the acetamido and thioacetamido groups, i.e., their preference for an equatorial/axial orientation. Thus, *trans*- and *cis*-1,2-diacetamidocyclohexanes and their mono- and dithio-analogues **1**–**6**, as well as their *N,N'*-dimethyl derivatives **7**–**12** (Scheme 1) were synthesized and studied by ^{1}H and ^{13}C NMR spectroscopy as well as by empirical force-field calculations. Compounds **1**, **3**, **5**, **7**, **9** and **11** were also obtained as optically active forms (*R,R*) by starting from (*R,R*)-



	R	X = Y = O	X = O, Y = S	X = Y = S
trans	H	**1**, *R*-**1**	**3**, *R*-**3**	**5**, *R*-**5**
cis	H	**2**	**4**	**6**
trans	Me	**7**, *R*-**7**	**9**, *R*-**9**	**11**, *R*-**11**
cis	Me	**8**	**10**	**12**

Scheme 1.

trans-diaminocyclohexane, while **4** and **10** were subjected to chromatographic enantiomer resolution on microcrystalline triacetylcellulose, in order to be studied by CD spectroscopy.

Experimental

Preparations. (±)-trans-*1,2-diacetamidocyclohexane* (**1**) *and* cis-*1,2-diacetamidocyclohexane* (**2**). **1** and **2** were prepared from the corresponding 1,2-diaminocyclohexanes (Aldrich, 0.035 mol) by reaction with acetic anhydride (0.08 mol) in ice-cooled chloroform (15 ml) for 1 h.[4] The white crystals formed were filtered off and recrystallized from ethyl acetate–ethanol (1:1). Yield quantitative, m.p. of **1** (*trans*) 260–263 °C, lit.[5] 258–260 °C; **2** (*cis*) 186–189 °C, lit.[5] 187–189 °C. IR (**1**): 1550, 1640, 3050, 3220, 3290 cm^{-1}; (**2**): 1560, 1640, 3080, 3220, 3310 cm^{-1}.

(*1*R,*2*R)-trans-*1,2-Diacetamidocyclohexane* (*R*-**1**) was prepared as above from the corresponding (1*R*,2*R*)-*trans*-1,2-diaminocyclohexane (Aldrich). Yield quantitative, m.p. 245–247 °C.

(±)-trans-*1-Acetamido-2-thioacetamidocyclohexane* (**3**) *and* (±)-trans-*1,2-bis(thioacetamido)cyclohexane* (**5**). **3** and **5** were obtained by refluxing **1** (2.0 mmol) in dry toluene (50 ml) with 2,4-bis(4-methylthiophenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (in the following denoted LR-3,[6] 1 mmol) for 24 h under an argon atmosphere. Flash chromatography using TLC grade silica gel (Merck, 60H) with light petroleum diluted with ethyl acetate as the eluent gave **3** as pale yellow crystals in 55% yield, m.p. 204–206 °C, and **5** as pale yellow crystals in 21% yield, m.p. 182–184 °C.

In another experiment, refluxing **1** (0.8 mmol) in dry toluene (50 ml) with LR-3 (2 mmol) for 24 h under a nitrogen atmosphere followed by flash chromatography as above with toluene–ethyl acetate (9:1) as the eluent gave **5** in 100% yield. HRMS for **3** gave M^+ 214.1139, calc. for $C_{10}H_{18}N_2OS$: 214.1140. HRMS for **5** gave M^+ 230.0916, calc. for $C_{10}H_{18}N_2S_2$: 230.0912. IR (**3**): 1100, 1150, 1180, 1350, 1370, 1390, 1440, 1460, 1540, 1650, 3200, 3260 cm^{-1}; (**5**): 1100, 1130, 1180, 1190, 1350, 1380, 1450, 1530, 3190 cm^{-1}.

(*1*R,*2*R)-trans-*1-Acetamido-2-thioacetamidocyclohexane* (*R*-**3**) *and* (*1*R,*2*R)-trans-*1,2-bis(thioacetamido)cyclohexane* (*R*-**5**). *R*-**3** and *R*-**5** were prepared as the racemic analogues, starting from *R*-**1**. *R*-**3**, m.p. 206–208 °C was obtained in 11% yield and *R*-**5**, m.p. 142–144 °C, in 78% yield based on recovered starting material (48%).

(±)-cis-*1-Acetamido-2-thioacetamidocyclohexane* (**4**) *and* cis-*1,2-bis(thioacetamido)cyclohexane* (**6**). Using **2** as the starting material, **4** and **6** were obtained as pale yellow crystals in the same way as **3** and **5** above, in 21% and 74% yield, respectively, m.p. 197–199 °C (**4**) and 147–148 °C (**6**). HRMS for **4** gave M^+ 214.1142, calc. for $C_{10}H_{18}N_2OS$: 214.1137. HRMS for **6** gave M^+ 230.0906, calc. for $C_{10}H_{18}N_2S_2$: 230.0912. IR (**4**): 1100, 1130, 1180, 1360, 1370, 1400, 1540, 1650, 3050, 3230, 3320 cm^{-1}; (**6**): 1100, 1170, 1380, 1530, 3040, 3200, 3300 cm^{-1}.

(±)-trans-N,N′-*Dimethyl-1,2-diacetamidocyclohexane* (**7**). A solution of **1** (15 mmol) in dry DMF (25 ml) was slowly added to an ice-cooled slurry of NaH (35 mmol) in dry DMF (10 ml). The mixture was stirred for 2 h at about 10 °C, then warmed to 40 °C and stirred at this temperature for 30 min. After cooling with ice–water, methyl iodide (35 mmol) was added, and the mixture was stirred for 1 h at about 10 °C and left to stir overnight at ambient temperature. DMF was removed under vacuum and the residue was washed with water and extracted with dichloromethane. On flash chromatography as above, **7** was obtained in 80% yield as colourless prisms, m.p. 88–90 °C. HRMS gave M^+ 226.1685, calc. for $C_{12}H_{22}N_2O_2$: 226.1681. IR: 1550, 1630 cm^{-1}.

(1*R*,2*R*)-*trans-N,N′*-Dimethyl-1,2-diacetamidocyclo hexane (*R*-**7**) was prepared essentially as above and was obtained as a yellow oil in 88% yield.

cis-N,N′-*Dimethyl-1,2-diacetamidocyclohexane* (**8**). **8** was prepared as for **7** with **2** as the starting material and was obtained as a pale yellow oil in 40% yield. HRMS gave M^+ 226.1681, calc. for $C_{12}H_{22}N_2O_2$: 226.1681. IR: 1630 cm^{-1}.

(±)-trans-N,N′-*Dimethyl-1-acetamido-2-thioacetamidocyclohexane* (**9**) and (±)-trans-N,N′-*dimethyl-1,2-bis(thioacetamido)cyclohexane* (**11**). **7** (2.0 mmol) was stirred with LR-3 (3.0 mmol) in dry 1,2-dimethoxyethane (25 ml) for 3 h under an argon atmosphere. Flash chromatography as above with hexane–toluene–ethyl acetate as the eluent gave **9** as a pale yellow oil in 4% yield and **11** as pale yellow crystals in 19% yield, m.p. 118–120 °C.

In another experiment, **7** (1.15 mmol) and LR-3 (1.725 mmol) in dry toluene (25 ml) were refluxed for 27 h under a nitrogen atmosphere. Flash chromatography as above with toluene–ethyl acetate (9:1) as the eluent gave **11** in 48% yield.

(*1*R,*2*R) - trans - N,N′ - *Dimethyl - 1 - acetamido - 2 - thioacetamidocyclohexane* (R-**9**) *and* (*1*R,*2*R)-trans-N,N′-*dimethyl-1,2-bis(thioacetamido)cyclohexane* (R-**11**). *R*-**9** and *R*-**11** were synthesized essentially as the racemic analogues and were obtained as a pale yellow oil in 7% yield and as pale yellow crystals in 39% yield, m.p. 137–138 °C, respectively. HRMS for *R*-**9** gave M^+ 242.1453, calc. for $C_{12}H_{22}N_2OS$: 242.1453. HRMS for **11** gave M^+ 258.1234, calc. for $C_{12}H_{22}N_2S_2$: 258.1224. IR (**9**): 1320, 1380, 1410, 1450, 1620 cm^{-1}; (**11**): 1280, 1410, 1490 cm^{-1}.

(±)-cis-N,N'-*Dimethyl - 1 - acetamido - 2 - thioacetamidocyclohexane* (**10**) *and* cis-N,N'-*dimethyl-1,2-bis(thioacetamido)cyclohexane* (**12**). **8** (1.0 mmol) in dry toluene (25 ml) was refluxed with LR-3 (0.6 mmol) for 20 h under an argon atmosphere. Flash chromatography as above gave **10** as a pale yellow liquid in 21% yield and **12** as pale yellow crystals in 63% yield, m.p. 120–121 °C. A similar experiment with a twofold molar excess of LR-3 gave a 92% yield of **12**. HRMS for **10** gave M^+ 242.1450, calc. for $C_{12}H_{22}N_2OS$: 242.1453. MS for **12** [IP 70 eV] *m/z* (% rel. int.): 258 (20, M^+), 225 (21), 193 (17), 169 (100), 140 (92), 127 (16), 114 (39), 58 (26), 56 (47). IR (**10**): 1260, 1340, 1400, 1480, 1630 cm^{-1}; (**12**): 1250, 1280, 1400, 1480 cm^{-1}.

Spectra. ^1H and ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer operating at 299.94 and 75.43 MHz for ^1H and ^{13}C, respectively, in $CDCl_3$ solution and at ambient temperature (ca. 300 K) unless indicated otherwise. Proton-coupled ^{13}C spectra were obtained in the gated-decoupling mode. Difference NOE (DNOE) ^1H spectra of the deoxygenated solutions were measured using a presaturation time of 10 s. 2D ^1H–^{13}C NMR correlation spectra were obtained using the standard Varian HETCOR software. Digital resolution in the ^1H and ^{13}C spectra was 0.2 and 1.0 Hz, respectively.

CD spectra were recorded with a JASCO Model J-500A spectropolarimeter, UV spectra with a Cary Model 2290 spectrophotometer, IR spectra with a Perkin-Elmer Model 298 spectrometer (KBr pellets), and high-resolution mass spectra (electron impact, direct inlet) with a JEOL SX-102 mass spectrometer.

Chromatographic resolutions of **4** and **10** were performed as described in Ref. 3 with the equipment described by Isaksson and Roschester.[7]

Empirical force-field calculations. The starting structures of compounds **1**–**12** were constructed with the Macintosh molecular modelling program MacMimic[8] and the energies were minimized with the Allinger MM2-91 force field.[9–11] The non-standard force constants used for the N–C=O and N–C=S frameworks have been published.[1,12]

Theoretical calculations of CD spectra were performed with the matrix technique devised by Schellman and co-workers.[13–16] This technique requires as input transition energies, strengths and directions of magnetic and electric transition dipoles, transition monopoles and quadrupoles, and static charges. Methods for the derivation of these data have recently been described,[17] and the results for the amide and thioamide chromophores are shown in Table 1. The static charges were taken from AM1 calculations on simple amides and thioamides.[18] Since the charges on the CNO(S) atoms predominate, and the other atoms are more distant, only the former charges have been included in the calculations. As discussed in Ref. 18, the precise values of the static charges are uncertain, but we expect the signs and the orders of magnitude to be correct.

Results and discussion

Empirical force-field calculations. The minimum-energy conformations of compounds **1**–**12** were explored by starting with minimizations from the chair forms with the (thio)acetamido groups in all combinations of *E* and

Table 1. Input data for theoretical calculation of CD spectra of $-C(=X)-NR_2$ (X = O and S). The charges are in units of the protonic charge.

Chromophore	ν/kK[a]	μ/D	*m*/BM[b]	α/°[c]	Δ/nm[d]	Monopole (coordinates/Å)	Static charge	Transition
Amide	45.66		0.8747		15.0			n→π*
O						0.1393 (±0.44)[e]	−0.36	
C							0.31	
N							−0.33	
	51.55	3.32		41	17.0			π→π*
O						0.2535		
C						0.0856		
N						−0.3391		
Thioamide	28.57		0.5295		28.0			n→π*
S						0.1687 (±0.60)[e]	−0.24	
C							0.04	
N							−0.26	
	36.23	2.67		16	18.0			π→π*
S						0.2396		
C						−0.1102		
N						−0.1294		

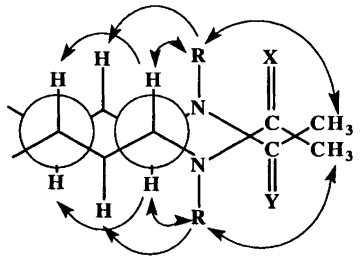
[a] 1kK = 1000 cm^{-1}. [b] Bohr magnetons. [c] See Fig. 5. [d] Half bandwith at 1/e of maximum Δε. [e] Quadrupole, *x,y* coordinates in plane perpendicular to the C=X bond.

Z forms, and with all unique combinations of C-2–C-1–N–C(=X) (θ_1) and C-1–C-2–N–C(=X) (θ_2) dihedral angles of +90° and −90° (see Scheme). In the *cis*-thioacetamido–acetamido compounds **4** and **10** the thioacetamido group may be axial or equatorial, and 32 different starting geometries were generated for each. For the other *cis* compounds and for the diequatorial conformers of the *trans*-thioacetamido–acetamido compounds **3** and **9**, 16 starting geometries resulted, which for the diequatorial conformers of the remaining *trans* compounds were reduced by symmetry to 12. Starting from geometries with other dihedral angles led to the same energy minima as from the above-mentioned starting geometries. Table 2 lists for each compound the minimum-energy conformations and those in the next 10 kJ mol^{-1} interval. A similar search of the boat-shaped cyclohexanes gave conformations at least 30 kJ mol^{-1} higher in energy than the corresponding chair form minima. Diaxial forms of the *trans-N*-methyl(thio)acetamido compounds **7**, **9** and **11** were also found to be at least 30 kJ mol^{-1} higher in energy than the diequatorial analogues, mainly due to unfavourable 1,3-diaxial interactions. For the NH analogues **1** and **3**, the diaxial forms were found to be disfavoured by 26 and 24 kJ mol^{-1} respectively, but in these cases a large part of the difference (21 kJ mol^{-1}) is due to N–H···O=C attractions (H-bonds in the MM2-91 program) and dipole–dipole attractions in the diequatorial form, which may be largely lost in a polar solvent like DMSO. In this solvent, therefore, observation of small amounts of diaxial forms of **1** and **3** is not unreasonable.

For the *trans-N*-methyl-(thio)acetamido compounds **7**, **9** and **11** and also for the dithio NH compound **5**, the most stable conformations are predicted to be *Z,Z* forms with antiparallel C=X groups (Fig. 1). These conformations are stabilized by dipole–dipole attraction and have been proposed in the earlier works in this series[1–3] to explain the prevalence of the *Z,Z* isomers of *N,N'*-dimethyl-1,2-bis(thio)acetamidoethanes. This conformation is, in the following, denoted form **A**. For the NH compounds **1** and **3**, a similar structure is predicted but with one (thio)acetamido group rotated to bring the NH

Table 2. Calculated steric energies and C1–C2–N–C (θ_1) and C2–C1–N–C (θ_2) dihedral angles for the most stable conformations of **1–12**. The *trans* compounds are in the *R,R* configuration, the mono-thio *cis* compounds **4** and **10** in the O(*R*), S(*S*) configuration.

Compd.	*E*/kJ mol^{-1}	θ_1	θ_2	(Thio)amide configuration
1	−47.1	83.5	148.5	*Z,Z*
2	−43.2	83.2	−146.5	*Z,Z*
	−37.8	146.1	77.0	*Z,Z*
3	−48.2	83.7	145.5	*Z,Z*
4	−44.1	84.9	−151.7	*Z,Z*, NHCSMe equatorial
	−39.0	148.3	77.4	*Z,Z*, NHCSMe axial
5	−37.4	100.8	100.2	*Z,Z*
6	−27.2	96.7	−141.7	*Z,Z*
	−24.0	109.1	−93.3	*Z*(eq), *E*(ax)
7	−2.2	111.3	111.3	*Z,Z*
	+5.4	115.4	126.1	*Z,E*
8	+25.6	104.3	−96.7	*Z*(eq), *E*(ax)
	+28.3	102.2	94.0	*Z,Z*
	+30.4	100.8	−97.6	*Z,Z*
	+31.8	104.4	−99.2	*E,E*
	+32.7	102.4	−96.0	*Z*(ax), *E*(eq)
9	+1.0	111.0	116.8	*Z,Z*
	+6.0	115.0	125.4	*Z,E*
	+9.2	126.9	121.6	*Z,E*
10	+27.9	105.2	−95.8	*Z*(eq), *E*(ax), NMeCOMe equatorial
	+28.9	105.3	−94.7	*Z*(eq), *E*(ax), NMeCOMe axial
	+32.8	104.3	−99.3	*E,E*, NMeCOMe axial
	+33.0	102.4	−96.6	*Z*(ax), *E*(eq), NMeCOMe axial
	+33.1	99.7	−95.0	*Z,Z*, NMeCOMe axial
	+33.3	−105.2	−91.3	*Z,Z*, NMeCOMe equatorial
11	+4.9	117.2	117.2	*Z,Z*
	+10.0	126.2	121.4	*Z,E*
12	+31.3	105.4	−95.1	*Z*(eq), *E*(ax)
	+35.3	105.0	−99.5	*E,E*
	+37.2	101.6	−96.9	*Z*(ax), *E*(eq)
	+37.4	100.8	−96.6	*Z,Z*



R = H, CH_3

X, Y = O, S

Fig. 1. Favoured conformation for the *trans* compounds **1**, **3**, **5**, **7**, **9** and **11** (form **A**), with indication of some of the NOE effects observed.

proton as close as possible to the carbonyl oxygen in response to the N–H···O=C attraction in the program. For all structures of compounds **1–4** reported in Table 1 the H···O distance is calculated to fall in the range 2.02–2.06 Å. No similar N–H···S=C attraction is included in the program although it is probably a real effect. However, it is likely to be considerably smaller than with amides. Studies of amides and thioamides in phenol and ethanol have shown that $-\Delta H$ for hydrogen bonding of amides is 5–8 kJ mol^{-1} higher than for the corresponding thioamides.[19] However, Dreiding models show that hydrogen-bonded dimers containing two NH···O(S)=C bonds can also be formed from conformers of type **A** (Fig. 1), and this may be a more likely explanation of the solvent effects found for the *trans* NH compounds in NMR and CD spectra (*vide infra*).

Calculations for the *cis* NH compounds **2**, **4** and **6** also predict the global minimum energy structures to be *Z,Z* isomers, but these do not have close-lying antiparallel C=X groups as predicted for the *trans* compounds. This structure, corresponding to form A, is, however, predicted for higher-energy minima. For **2** and **4** this form is only ca. 5 kJ mol^{-1} above the global minimum, whereas for **6** the difference is 9.2 kJ mol^{-1}.

Calculations for the *cis* *N*-methyl compounds **8**, **10** and **12** predict several close-lying energy minima, but the global minimum is uniformly a *Z*(eq), *E*(ax) conformation. The *Z,Z* form with antiparallel C=X groups is only 2.7 kJ mol^{-1} above the global minimum for **8**, whereas the difference is 5.4 kJ mol^{-1} for **10** and 15.1 kJ mol^{-1} for **12**.

For the mono-thio *cis* compounds **4** and **10** there is the choice between axial or equatorial thioacetamido groups. The latter is preferred for both compounds.

NMR results. 1. trans- *and* cis-*1,2-diacetamidocyclohexanes and their mono- and dithio-derivatives* **1–6**. The ^1H and ^{13}C NMR parameters for compounds **1–6** are presented in Table 3. The signal assignments were in accord with previous data for structurally similar compounds[1–3] and were verified by selective decoupling and ^1H DNOE experiments. The ^{13}C assignments were also supported by the signal multiplicities observed in the gated-decoupled spectra, as well as by the values of the one-bond ^{13}C–^1H coupling constants[20] (139–141 Hz when the respective carbon was N-bonded, and 128–130 Hz when it was C-bonded). Unlike some *N*-methyl(thio)amides studied earlier[1,2] and analogous to what was found for *N,N'*-di(thioacetyl)-N,N'-dimethyl-1,2-diamino-1,2-diphenylethanes,[3] the NMR spectra of all NH-compounds **1–6** showed signals of one single configurational isomer with respect to the (thio)amide C–N partial double bond. It was expected that this isomer would be the *Z,Z* form, as predicted by the molecular mechanics calculations (Table 2). This prediction was proved correct by the ^1H DNOE spectra, which showed strong enhancements of the CH_3 signals upon irradiation of the vicinal NH group and *vice versa*.

The *trans*-compounds **1**, **3** and **5** were expected to exist predominantly or exclusively as conformers with diequatorially located substituents. This was clearly shown to be the case by the values of the vicinal proton–proton coupling constants of the two CH-groups in **3** measured upon selective decoupling of the respective vicinal NH-proton. While under such circumstances the CH-signals of **1** and **5** still remain complex multiplets, each of the two CH-signals of **3** was observed as a triplet of doublets, with a large splitting of 10.8–11.0 Hz and a small one of ca. 3.5 Hz. Using the Haasnoot equation,[21] the following values of the vicinal coupling constants (Hz) were calculated for the lowest-energy (diequatorial) conformer of **3**: J(H-1a,H-2a) = 10.6, J(H-1a,H-6a) = 11.8, J(H-1a,H-6e) = 3.6, J(H-2a,H-3a) = 11.8 and J(H-2a,H-3e) = 3.8. The values calculated for **1** and **5** are very similar. Thus, a predominant diequatorial conformation is clearly demonstrated for these compounds.

The results from DNOE experiments on the *trans*-compounds **1**, **3** and **5** confirmed the diequatorial *Z,Z* conformation, but they also yielded some valuable information concerning the conformational preference with respect to the CH–NH bond. In this respect the 'mixed' *trans*-compound **3** was of particular value, since it provided separate signals for most of the proton groups, including some of the ring protons (Table 3). Thus, irradiation of NHCS led to signal enhancements of CH_3CS, H-1 and another ring proton, which was assigned as H-3a. When H-2 was irradiated, positive NOEs were observed for NHCO, H-3e and two more ring protons, which were assumed to be H-4a and H-6a. Similar enhancements were also observed when the corresponding protons of the 'O-part' of the molecule were irradiated. Thus, the favoured conformation of the *trans*-compounds **1**, **3** and **5** deduced on the basis of the NMR data is form A shown in Fig. 1 (R = H). The conformation is similar to that deduced for (*R,R*)-*trans*-*N,N'*-di(5-bromosalicylidene)-1,2-cyclohexanediamine on the basis of CD-spectra,[22] as well as with that predicted for *N,N'*-dimethyl-*N,N'*-di(thioacyl)-1,2-diaminoethanes from force-field (MM1) calculations.[1]

As discussed above, the conformational arrangement might permit intramolecular NH···O(S)=C hydrogen bond formation, and a hydrogen-bonded dimer is also feasible. In order to investigate the possibility of hydro-

Table 3. ^{1}H and ^{13}C NMR chemical shifts (ppm) and coupling constants (Hz, in parentheses) for compounds **1–6** in $CDCl_3$.

Compd.	Config.	Nucl.	*CH*$_3$CO	*CH*$_3$CS	*CH*NCO	*CH*NCS	CH_2	N*H*CO	N*H*CS
1	*trans*	^{1}H	1.94 s		3.64 m		1.31 (4 H) m, H-3a,4a,5a,6a; 1.74 (2 H) m, H-4e,5e; 2.00 (2 H) m, H-3e,6e	6.1 br s	
		^{13}C	23.37		53.92		24.72, C-4,5; 32.22, C-3.6	170.87	
2	*cis*	^{1}H	2.01 s		4.01 m		1.51 (6 H) m, H-3a,6a; 1.85 (2 H) m H-3e,6e	6.3 br s	
		^{13}C	23.67		50.80		22.17, C-4,5; 28.46, C-3,6	171.03	
3	*trans*	^{1}H	1.95 s	2.49 s	3.83 m	4.28 m	1.20–1.40 (4 H) m, H-3a,4a,5a,6a; 1.79 (2 H) m H-4e,5e; 2.00 (1 H) m, H-6e; 2.29 (1 H) m, H-3e	6.18 d (6.3)	8.45 br s
		^{13}C	23.43	34.29	53.52	60.40	24.24, C-5;[a] 24.78, C-4;[a] 30.36, C-6; 32.08, C-3	171.41	201.07
4	*cis*	^{1}H	2.09 s	2.52 s	4.19 m	4.36 m	1.30–1.75 (6 H) m, H-3a,6a,4,5; 1.82 (1 H) m, H-6e; 2.28 (1 H) m, H-3e	5.87 br d (5)	9.12 br s
		^{13}C	23.67	34.62	49.94	58.83	20.73,C-5; 23.39,C-4; 24.86,C-6; 29.65,C-3	172.51	200.41
5	*trans*	^{1}H		2.49 s		4.53 m	1.36 (4 H) m, H-3a,4a,5a,6a; 1.81 (2 H) m, H-4e,5e; 2.21 (2 H) m, H-3e,6e		8.20 br s
		^{13}C		34.55		59.87	24.30,C-4,5; 30.70, C-3,6		201.65
6	*cis*	^{1}H		2.58 s		4.80 m	1.45–1.78 (6 H) m, H-3a,6a,4,5; 2.15 (2 H) m, H-3e,6e		8.04 br s
		^{13}C		35.01		56.45	22.11, C-4,5; 27.27, C-3,6		202.15

[a] Assignments may be interchanged.

gen bonds playing some role in the determination of the conformational distribution, ^{1}H NMR studies of the *trans* compounds **3** and **5** were also carried out in ($^2H_6$)DMSO solutions. Except for the expected deshielding of the NH-signals by ca. 1.5 ppm, no major changes in the chemical shifts, compared with solutions in $CDCl_3$ (Table 3) were observed. Upon spin-decoupling of NH, both CH-signals of **3** again appeared as triplets of doublets, with apparent couplings of 10.0–10.5 Hz and 4 Hz. This small decrease of the *anti*-coupling in ($^2H_6$)DMSO, compared with that in $CDCl_3$, might indicate a slight shift in the conformational equilibrium towards the diaxial conformer (estimated to be present in less than 10%), as a result of the elimination of the intramolecular H-bonding. Similar conclusions can also be drawn from the values of the CH–NH couplings [8.5 Hz in ($^2H_6$)DMSO vs. 6.3 Hz in $CDCl_3$ for **3**], although this parameter is less reliable owing to the large broadening of the NH signals. The NOE measurements for **3** in ($^2H_6$)DMSO yielded essentially the same results as in $CDCl_3$. As discussed in the section on force-field calculations, the presence of a small amount of diaxial conformer is not in conflict with the results of the computations. On the other hand, the ^{1}H NMR spectra in ($^2H_3$)acetonitrile are quite similar to those in $CDCl_3$ solution.

For the conformational analysis of the *cis* compounds **2**, **4** and **6**, again the 'mixed' compound **4** was most useful. Spin decoupling of NHCS turned the signal for H-2 into a triplet of doublets (J=10.3, 2.5 Hz), thus indicating a strong preference of the $NHCSCH_3$ group for an equatorial orientation. Correspondingly, under the same conditions H-1 appeared roughly as a quartet with a splitting of ca. 3 Hz. DNOE experiments showed that both substituents have the *Z* configuration: irradiation of NH enhanced the vicinal CH_3C proton signal, and *vice versa*. Irradiation of NHCS influenced largely H-1 but also H-2, whereas irradiation of NHCO led to an increased signal intensity of H-1 as well as of another ring proton signal, most probably H-5a, but not of H-2. Accordingly, irradiation of H-1 affected both NH proton signals, while irradiation of H-2 enhanced the signal of NHCS (as well as of some ring protons, probably H-4a and/or H-6a), but not NHCO. Thus, the ^{1}H NMR evidence (selective decoupling plus DNOE) was in favour of a conformation with equatorial *Z*-$NHCSCH_3$ and axial *Z*-$NHCOCH_3$ groups, having the NHCS hydrogen and the CO oxygen close to each other and in all probability forming an intramolecular hydrogen bond, in quite satisfactory agreement with the results of the force-field calculations. This conformation is shown in Fig. 2. In accord with these conclusions, the following couplings were obtained from the NH-signals in ($^2H_6$)DMSO solution: J(CH–NHCS)=6.6 (in $CDCl_3$ broad unresolved signal); J(CH–NHCO)=8.9 Hz (in $CDCl_3$ ca. 5 Hz). In ($^2H_6$)DMSO, selective decoupling of NH left the H-2 signal still as a doublet of triplets, but with somewhat smaller *anti* coupling (J_{anti}=9.3, J_{gauche}=2.5 Hz); H-1 changed to an unresolved multiplet with larger half-width as compared with its appearance in $CDCl_3$. Thus, one may conclude that in the more polar solvent the preference of $NHCSCH_3$ (as compared to $NHCOCH_3$) for an equatorial orientation is retained, albeit slightly reduced.

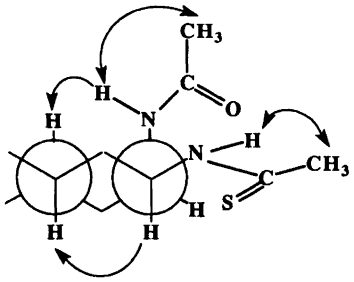


Fig. 2. Favoured conformation for the *cis* compound **4**, with indication of some of the NOE effects observed.

The NMR study of the symmetric *cis*-compounds **2** and **6** yielded essentially the same results as already discussed for **4**, thus indicating favoured conformations corresponding to Fig. 2, in agreement with the force-field calculations.

In the case of *cis*-compound **6** only, additional weak signals were observed for the NH and the CH_3CO groups in the ^{1}H as well as in the ^{13}C spectra, indicating the presence of another stereoisomer, most probably a *Z,E* form, as predicted by the force-field calculations (Table 2). The calculations predict 22% of the minor isomer at 25 °C, whereas the integrals give only 5%. Anyhow, the conclusion is that thioamide groups are somewhat less comfortable in an axial *Z* orientation than are amide groups, in accord with the observations for the *N*-methylated derivatives discussed below. A generally diminished preference for the *Z* form in *N*-methylthioamides compared with *N*-methylamides has been observed.[23]

The chemical shift values summarized in Table 3 are in accord with the proposed configurations and conformations of the compounds. It is well known[21] that in cyclohexane systems axial protons usually resonate at higher field than the equatorial ones. This is reflected by the proton chemical shifts (δ-values) of the CH-protons which are smaller for the *trans* than for the *cis* forms (purely axial protons); the same trend is observed for the ring methylene protons (Table 3). On the other hand, the chemical shifts of the methine carbons are larger for the *trans* isomers, which are supposed to be less crowded. The proton and carbon chemical shift values of the CH_3CO and CH_3CS groups are close to those observed for the acyclic analogues.[1–3]

2. trans- *and* cis-N,N′-*Dimethyl-1,2-di(thioacetamido)-cyclohexanes* **7–12**. The ^{1}H and ^{13}C NMR parameters for compounds **7–12** are presented in Table 4. The procedures used for obtaining the spectra and for signal assignments were similar to those described above.

For the *trans* compounds **7**, **9** and **11**, the NMR

Table 4. ^{1}H and ^{13}C NMR chemical shifts (ppm) and coupling constants (Hz, in parentheses) for compounds **7–12** in $CDCl_3$.

Compd.	Config.	Nucl.	CH_3CO	CH_3CS	CH_3NCO	CH_3NCS	CHNCO	CHNCS	CH_2	CO	CS
7	*trans*	^{1}H	2.03 s		2.81 s		4.65 m		1.2–1.6 (4 H) m, H-3e,4e,5e,6e; 1.65–1.9 (4 H) m, H-3a,4a,5a,6a		
		^{13}C	22.47		30.78		51.82		25.00, C-4,5; 29.27, C-3,6	170.76	
8	*cis*	^{1}H	2.00 s[a]		2.86 s		4.63 dt (10.0, 4.4)				
			2.08 s[b]		3.11 s		4.22 td (4.3, 1.8)		1.5–2.1 (8 H) m, H-3,4,5,6		
			2.04 s[c]		3.02 s		4.7 m				
		^{13}C	21.29[a]		31.93		53.98		22.02, C-5;[d] 24.90, C-4;[d]	171.16[d]	
			22.24[b]		32.01		52.88		26.18, C-6;[d] 28.63, C-3[d]	171.59[d]	
			22.62[c]		34.24		52.15		23.68,[e] 27.01[e]	171.30[c]	
9	*trans*	^{1}H	2.05 s	2.60 s	2.89 s	3.05 s	4.77 dt (11.3, 4.2)	5.76 dt (11.4, 4.1)	0.8–2.0 (8 H) m, H-3,4,5,6		
		^{13}C	22.46	33.66	31.61	34.47	52.52	60.41	24.68, C-5; 24.89, C-4	170.98	200.37
10	*cis*	^{1}H	2.02 s[c]	2.59 s	3.15 s	3.05 s	4.55 br t (4.8)	5.60 dt (13.2, 4.6)			
			2.07 s[g]	2.59 s	2.82 s	3.60 s	4.73 m	4.68 m	1.5–2.1 (8 H) m, H-3,4,5,6		
			1.98 s[f]	2.56 s	3.03 s	3.19 s	4.85 m	5.90 m			
		^{13}C	21.59[f]	33.30	32.28	35.47	50.49	62.56	21.59,[f] 21.46,[g] C-5, 24.89,[f]	171.48[d]	201.29[d]
			22.17[g]	32.33	31.73	40.56	52.99	56.94	24.50,[g] C-4; 26.17,[f] 25.50,[g]	171.93[d]	201.79[d]
			23.00[c]	33.89		36.61	51.40	59.84	C-6; 28.50,[f] 27.89,[g] C-3; 23.10,[e] 23.71,[e] 26.72,[e] 27.05[e]		
11	*trans*	^{1}H		2.60 s[c]		3.10 s		5.93 m	1.4–1.6 (4 H) m, H-3a,4a,5a,6a;		
				2.52 s[a,h]		3.19		5.85	1.83 (2 H) m, H-4e,5e;		
				2.69 s[b,h]		3.04		4.30	1.92 (2 H) m, H-3e,6e		
				2.68 s[h,i]		3.17					
		^{13}C		33.79		35.21		60.79	24.67, C-4,5; 28.04, C-3,6		200.79
12	*cis*	^{1}H		2.60 s[a]		3.01 s		5.74 ddd (13.0,5.4,4.2)	0.8–2.1 (8 H) m, H-3,4,5,6		
				2.62 s[b]		3.67 s		5.00 br t (5.4)			
				2.59 s[c]		3.25 s		6.25 m			
		^{13}C		33.36[a]		35.24		61.51	21.05, C-5;[d] 24.62, C-4;[d]		201.92[d]
				32.82[b]		40.89		54.78	25.51, C-6;[d] 27.86, C-3;[d]		202.39[d]
				34.09[c]		36.90		58.02	22.87;[e] 26.54[e]		202.50[c]

[a] *E,Z* isomer, *Z* part. [b] *E,Z* isomer, *E* part. [c] *Z,Z* isomer. [d] *E,Z* isomer. [e] Unassigned signals from *Z,Z* isomer. [f] *E,Z* isomer, CH_3CS equatorial (E_OZ_S). [g] *E,Z* isomer, CH_3CS axial (E_SZ_O). [h] Solvent ($^{2}H_3$)acetonitrile. [i] *E,E* isomer.

spectra were again dominated by the signals of the *Z,Z* forms. For all these compounds however, additional signals for two more isomers were observed in the ^{1}H as well as the ^{13}C spectra, amounting to ca. 5 and 3% of the major form, respectively, according to the integrals of the proton signals. The MM2(91) calculations predict one or two *E,Z* conformers to be close in energy to the major conformer. Only **9** can accommodate two minor *E,Z* isomers with slow exchange on the NMR timescale, and for **7** and **11** one of the minor forms is an *E,Z* and the other an *E,E* isomer.

The CH-signals were analysable only in the case of **9**. Each of H-1 and H-2 gave a triplet of doublets, with splittings of 11.4 and 4.1 Hz. These values exclude the presence of significant amounts of a diaxial invertomer in the major steroisomer of **9**, and probably also in those of the other *trans* compounds **7** and **11**. The DNOE studies of **9** confirmed the *Z,Z* configuration of the predominant isomer and suggested a favoured conformation of type **A**, (Fig. 1, R = CH_3). Thus, irradiation of H-2 enhanced CH_3NCO and *vice versa*; the same was true for H-1 and CH_3NCS. Mutual enhancement was observed also for the CH_3N and CH_3C protons in the same substituent.

Interesting effects caused by the increased steric hindrance were observed for the *cis* compounds **8**, **10** and **12**. Their ^{1}H and ^{13}C NMR spectra exhibited a double number of strong signals as compared with all other compounds discussed so far (Table 4 and Fig. 3, spectra on top and to the right). A detailed analysis of the normal, spin-decoupled, DNOE and two-dimensional hetero-correlated NMR spectra of all *cis*-compounds led to the conclusion that the predominant isomer is the *Z*(equatorial), *E*(axial) form, or two such forms in the case of **10**. This conclusion was also supported by the results of the force-field calculations (Table 2).

Integration of the proton signals of compound **10** revealed that three isomers (f, g and c, Fig. 3) were present in the ratio 56:33:11. The predominant isomer was assigned as an *E,Z* form with *Z*-equatorial $CH_3CSN(CH_3)$ and *E*-axial $CH_3CON(CH_3)$ substituents (designated E_OZ_S), the second one as an *E,Z* form with *Z*-equatorial $CH_3CON(CH_3)$, *E*-axial $CH_3CSN(CH_3)$ substituents (designated E_SZ_O), and the third one as a *Z,Z* form. In the two major isomers, the axial substituent is *E*-oriented. The assignments were based mainly on the proton CH-signal appearance and on the DNOE evidence, as well as on chemical-shift comparison with related compounds where such isomers have also been observed.[1,2] Thus, the strongest pair of CH signals of **8** and **10** appeared as a lower-field doublet of triplets and for **12** as a doublet of doublets of doublets, with splittings of 10.0–13.2 and 4–5 Hz (axial proton), and a higher-field triplet of doublets (4.3–5.4 and 1.8 Hz, equatorial

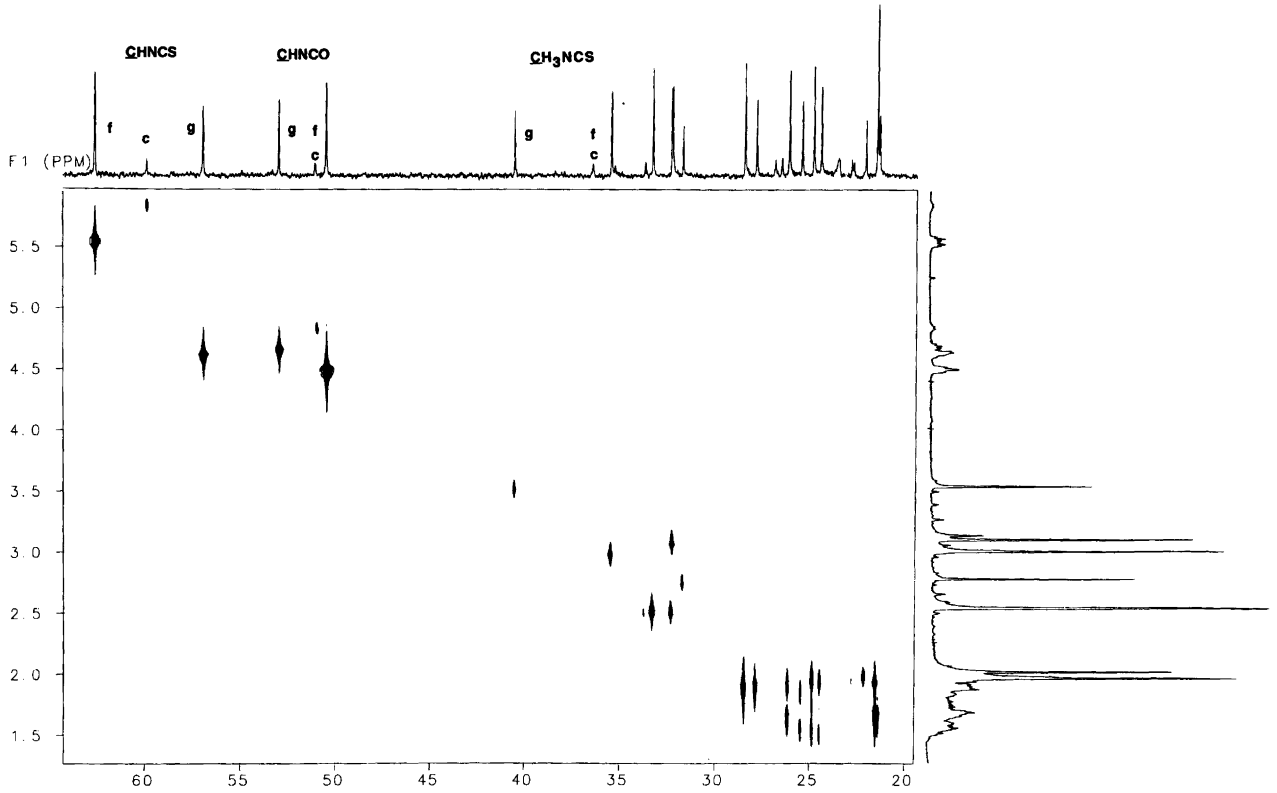


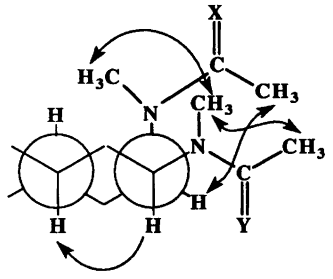
Fig. 3. 2D ^{1}H–^{13}C NMR shift correlation spectrum of compound **10** in $CDCl_3$ at 300/75 MHz, showing the ^{1}H and ^{13}C spectra in the vertical and horizontal directions, respectively, as well as the corresponding cross-peaks. The assignments of the CHNCS, CHNCO and CH_3NCS carbons of the observable isomers are indicated as in Table 4: c – *Z,Z*-form; f – *E,Z*-form, CH_3CS equatorial; g – *E,Z*-form, CH_3CS axial. For the other signal assignments, see Table 4 and the text.

proton). Irradiation of the lower-field CH-signals in **10** and **12** led to no CH_3 signal enhancement, whereas irradiation of the higher-field CH enhanced the CH_3C proton resonance of the respective substituent, thus proving its *E* orientation. Irradiation of the CH_3NCS resonance of the E_OZ_S form led to an intensity increase of the resonance of the corresponding *Z*-oriented CH_3CS group. Important evidence concerning the conformation about the CH–N(CH_3) bond was obtained in the case of compound **12** from the mutual enhancement of the CH_3N signals of the two substituents as well as by the enhancement of some ring proton signals (Fig. 4) upon irradiation of each of the former signals. On the basis of all this evidence, it was concluded that the favoured conformation of the *E,Z* forms in **8**, **10** and **12** should resemble that in Fig. 4, in agreement with the results from the force-field calculations (Table 2).

The proton and carbon chemical shifts of the CH_3 groups (Table 4) were similar to those observed for the NH-compounds (Table 3) as well as for other related compounds.[1-3] The well-known anisotropy of the C=S group[24] leads to deshielding of the CH_3NCS protons in the *E* part of the *E,Z* isomers of **10** and **12** and to a large shift difference between H-1 and H-2 in the E_O,Z_S isomer of **10** and to a small shift difference in the E_S,Z_O isomer. The assignment of the third isomers of **10** and **12** to the *Z,Z* form is based on the low-field positions of the H-1 and H-2 resonances (Table 4).

CD and UV spectra. All *trans* compounds are chiral, and so are the *cis* compounds **4** and **10** because of the unequal substituents in positions 1 and 2. UV spectra have been recorded for all of the compounds and CD spectra for compounds *R*-**1**, *R*-**3**, *R*-**5**, *R*-**7**, *R*-**9** and *R*-**11**, and also for the enantiomers of **4** and **10** which were eluted first on chromatography on triacetylcellulose. The results are found in Table 5.

The chromophores responsible for the UV and CD absorption are the amide and/or the thioamide groups. It follows from the data in Table 6 that amides have a weak band in the neighbourhood of 220 nm, shifted to shorter wavelengths in more polar solvents and even more in hydroxylic solvents, where it is completely obscured by a stronger band in the range 180–196 nm,



X, Y = O, S

Fig. 4. Favoured conformation for the *E,Z* forms of the *cis* compounds **8**, **10** and **12**, with indication of some of the NOE effects observed.

less sensitive to solvent polarity than the weak band. Both bands undergo bathochromic shifts with increasing *N*-substitution. The weak band is assigned to an $n\rightarrow\pi^*$ and the stronger to the first $\pi\rightarrow\pi^*$ transition.

The polarization of the $\pi\rightarrow\pi^*$ transition is defined by the angle α in Fig. 5. Peterson and Simpson[29] found a polarization corresponding to $\alpha=41°$ in a study of polarized spectra of single crystals of myristamide. In a recent, very careful study Clark[25] found $\alpha=35\pm3°$ for propanamide and $\alpha=55\pm5°$ for *N*-acetylglycine. CNDO/S calculations give $\alpha=8°$ for acetamide, 15° for *N*-methylacetamide and 16° for *N,N*-dimethylacetamide. In the theoretical calculations of CD spectra we used the value 41° and recalculated the transition charges obtained for *N,N*-dimethylacetamide to the new polarization direction by the Lagrange multiplier method proposed by Rizzo and Schellman.[30] The transition charges were then scaled to conform with the transition moment obtained from the experimental absorption spectrum.

The thioamide chromophore gives a weak $n\rightarrow\pi^*$ band at ca. 350 nm and a medium–strong $\pi\rightarrow\pi^*$ band at ca. 270 nm. In addition, a weaker band (ε ca. 5000) is often observed near 220 nm. Hosoya *et al.*[31] found the polarization of the 270 nm band in thioacetamide to correspond to $\alpha=16°$. Since a CNDO/S calculation for *N,N*-dimethylthioacetamide gave $\alpha=14°$, the transition charges from this calculation were used directly after scaling as above. Based on *ab initio* random phase approximation calculations Kajtar *et al.*[32] assigned the 220 nm band to a transition from a low-lying sulfur lone pair orbital with some C–S σ character to the lowest π^* orbital ($n_\sigma\rightarrow\pi^*$).

The UV spectrum of *R*-**3** (Table 4) shows a shoulder at 218 nm ($\varepsilon=3600$) but no distinct CD band in the same range, and *R*-**11** shows a stronger shoulder at 212 nm ($\varepsilon=10\,600$) and a corresponding strong CD couplet centered at 220 nm. The other thioamides show only non-selective medium–strong absorption in this region. These effects might be due to the $n_\sigma\rightarrow\pi^*$ transition discussed above. A CNDO/S-CI calculation without d orbitals for *N,N*-dimethylthioacetamide predicts a weak $n\rightarrow\pi^*$ transition at 491 nm and a strong $\pi\rightarrow\pi^*$ transition 261 nm. The third transition is between an n_σ type orbital in the C=S bond and the lowest π^* orbital, but the predicted oscillator strength (*f*) is only 0.00023, and the polarization is perpendicular to the thioamide plane. It is therefore an unlikely candidate for a transition responsible for absorption in the range $\varepsilon=3000$–7000. Unfortunately, no data on the polarization of the $n_\sigma\rightarrow\pi^*$ transition discussed in Ref. 32 have been published. Provisionally, we denote this excitation *transition 3*. If we assume $\lambda_{max}=220$ nm, $\varepsilon_{max}=5000$ and the exponential half-bandwidth $\Delta=15$ nm, we arrive at a transition moment for transition 3 of 2.36 D. Because of its strength, this transition should be polarized in the thioamide plane.

The analysis of the CD spectra with aid of theoretical calculations based on the predicted minimum-energy

Table 5. Experimental UV spectra and experimental and theoretical CD spectra of compounds **1**–**12**. Solvent acetonitrile.

Compound		λ_{max}/nm (ε,$\Delta\varepsilon$/M^{-1} cm^{-1})
1 (UV)		198 (12 000)
R-**1** (CD)	Exp.	219 (−1.09), 198 (+2.17)
	Calc.	216 (+4.09), 195 (−4.69)
2 (UV)		198 (12 500)
3 (UV)		324 (70), 267 (10 500), 218sh[a] (3 600)
R-**3** (CD)	Exp.	340 (+0.84), 291 (−0.93), 265.5 (+9.9), 205 (−9.1)
	Calc.	350 (+0.51), 276 (−1.74), 220 (+3.53), 194 (−2.26)
4 (UV)		334 (54), 267 (11 200)
4 (CD)[b]	Exp.	333 (−1.5), 265 (+26.0), 208 (−21)
	Calc. conf. 1	350 (−0.14), 276 (+0.26), 222 (+3.87), 194 (−2.84)
	Calc. conf. 2	350 (+1.09), 276 (−2.72), 220 (+3.96), 194 (−2.21)
5 (UV)		330sh (120), 268 (27 900), 200sh (8 200)
R-**5** (CD)	Exp.	338 (+1.5), 268 (+14.0), 206 (−10.0)
	Calc.	350 (+4.52), 282 (−17.8), 268 (+7.06)
6 (UV)		324sh (120), 264 (18 500)
7 (UV)		198 (13 400)
R-**7** (CD)	Exp.	212 (+8.8), 191 (−7.5)
	Calc.	217 (+5.64), 194 (−4.48)
8 (UV)		198 (12 400)
R-**9** (UV)		344sh (70), 273 (13 900), 195[c] (14 100)
R-**9** (CD)	Exp.	350 (+2.52), 280 (−0.8), 222 (+5.1)
	Calc.	350 (+1.41), 276 (−1.90), 222 (+1.85), 194 (−1.51)
10 (UV)		325sh (120), 273 (14 400), 195[c] (13 000)
10 (CD)[b]	Exp.	350 (−0.86), 278 (+3.90), 205 (−2.2)
	Calc. conf. 1[d]	350 (−0.19), 276 (+7.08), 202 (−1.57)
	Calc. conf. 2[d]	350 (+0.38), 276 (−7.64), 198 (+2.00)
11 (UV)		350 (160), 276 (35 300), 212 (10 600)
R-**11** (CD)	Exp.	354 (+9.1), 285 (+7.00), 264 (−13.6), 231 (+10.3), 208.5 (−17.3)
	Calc. isomer A	350 (+2.73), 276 (−4.75)
	Calc. isomer B	350 (+0.50), 284 (+27.5), 268 (−25.9)
12 (UV)		343 (110), 274 (25 500), 200sh (9 800)

[a] Shoulder. [b] First eluted enantiomer. [c] End absorption. [d] 1*S*,2*R* configuration.

Table 6. UV spectra of representative amides and thioamides.

Compound	Solvent	λ_{max}/nm (ε/M^{-1} cm^{-1})	Ref.
Propanamide	$(MeO)_3PO$	220 (75), 180 (7000)	25
N-Acetylglycine	$(MeO)_3PO$	213 (220sh[a]), 185 (7000)	25
Acetamide	Water	182 (7600)	26
N-Methylacetamide	Water	186 (8800)	26
	Dioxane	224 (90)	26
	Cyclohexane	227 (44), 184 (5400)	26
N,*N*-Dimethylacetamide	Water	196 (9350)	26
	Dioxane	232 (129)	26
	Cyclohexane	233 (110), 196 (6850)	26
Thioacetamide	Heptane	367 (35), 267 (13800) 231 (5900)	27, 28
	Ethanol	327 (51), 266 (12600) 210 (4300)	27, 28
N,*N*-Dimethylthioacetamide	Heptane	365 (41), 272 (15500) 219 (5000)	28

[a] sh = shoulder.

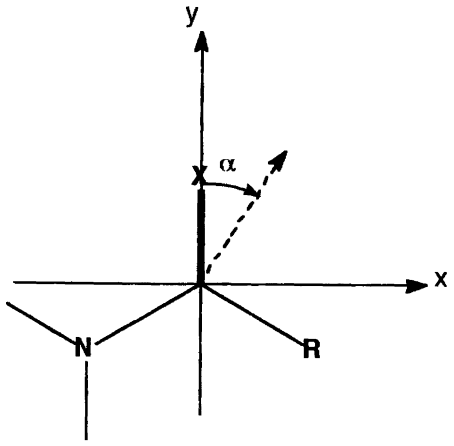


Fig. 5. Direction of the first π→π* transition in amides and thioamides.

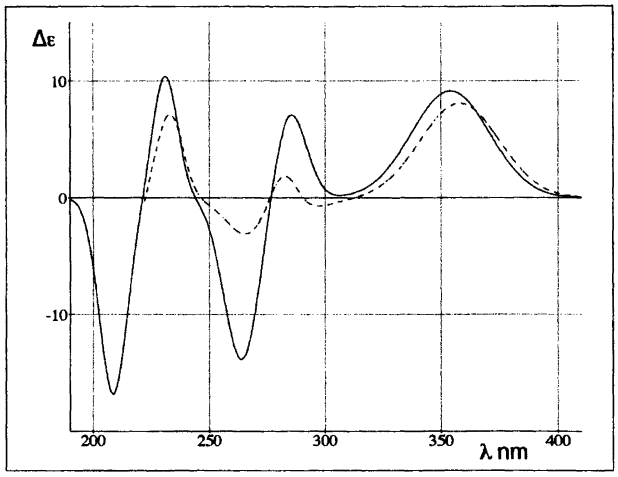


Fig. 6. CD spectrum of *R*-**11** in dichloromethane (– – –) and in acetonitrile (—).

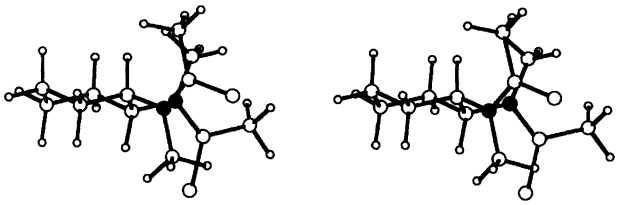


Fig. 7. Stereopicture of conformation **B** of *R*-**11**.

conformations is most straightforward for the *trans-N*-methyl compounds *R*-**7**, *R*-**9** and *R*-**11**. The CD spectrum of *R*-**7** shows a negative band at 191 nm and a positive band of similar strength at 212 nm. Calculation with a geometry taken from the form **A** predicted by the MM2-91 calculations to be the global energy minimum (Table 2 and Fig. 1) predict a CD spectrum quite similar to the experimental one (Table 5). Analysis of the calculations shows that the coupled oscillator mechanism contributes only a little to the rotational strength, since the π→π* transition moments are nearly antiparallel. The m-μ and one-electron mechanisms contribute each about twice as much to the rotational strength, which explains the nearly symmetric couplet character of the spectrum.

The long-wavelength part of the CD spectrum of *R*-**9**, with a positive n→π* and a weak negative π→π* thioamide transition, is well reproduced by the calculation. The positive band at 222 nm in the experimental spectrum may have its origin in the amide n→π* transition, calculated to be positive, and transition 3, probably also positive. A weak negative amide π→π* band is predicted at 194 nm, but no corresponding band is observed.

The CD spectrum of *R*-**11** calculated with the geometry of form **A** is predicted to show a rather strong positive n→π* band at 350 nm and a single negative π→π* band at 276 nm. The experimental spectrum (Fig. 6) contains two bands with signs in agreement with those calculated, at 354 and 264 nm. In addition, it contains a positive band at 285 nm and a positive couplet centred at 220 nm. The band at 285 nm is at first unexpected, since no couplet is predicted from the π→π* transitions. However, as mentioned above, the NMR spectra in $CDCl_3$ solution show the presence of one *E,Z* and one *E,E* form in amounts of 5 and 3%, respectively. The theoretical CD spectrum of the stereoisomer predicted to be second in stability (isomer **B**, Fig. 7) consists of a positive n→π* band at 350 nm (Δε = +0.5) and a positive couplet (+27.5; −25.9) centred at 276 nm. The experimental spectrum in the region 250–310 nm may be composed of a weak negative π→π* band from isomer **A** and a positive couplet from isomer **B**. The amount of isomer **B** present in $CDCl_3$ solution is too small to account for the positive CD band at 285 nm in acetonitrile solution. However, MM2-91 calculations predict the dipole moment of isomer **B** to be 6.13 D and that of isomer **A** to be 0.98 D, and the former should be favoured by polar solvents. In agreement with this, a ^1H NMR spectrum of **11** in ($^2H_3$)acetonitrile showed the ratio *Z,Z*(**A**): *E,Z*(**B**): *E,E* = 75:22:3. Conversely, the CD spectrum of **11** recorded in dichloromethane solution (Fig. 6) showed a much reduced intensity of the couplet centred at 275 nm, and, in addition a weak negative band at 297 nm, which can be interpreted as the long-wavelength residue of a broad, rather weak negative band centred at 278 nm, the π→π* band of form **A**. The positive couplet centred at 275 nm is ascribed to isomer **B**.

The positive couplet centred at 220 nm is assigned to transition 3. It has a lower intensity in dichloromethane than in acetonitrile solution, and it should therefore have its largest contribution from isomer **B**. A model calculation was carried out to try to find the polarization direction (α) of this transition, assumed to lie in the thioamide plane. The transition moment was assumed to be 2.36 D, and the transition charges were taken from the first π→π* transition (Table 1) and scaled to conform to the smaller transition dipole. Calculations were performed for α in steps from −90° to +90°, and for each α value new transition charges were obtained by the Lagrange multiplier technique.[30] Geometries were taken

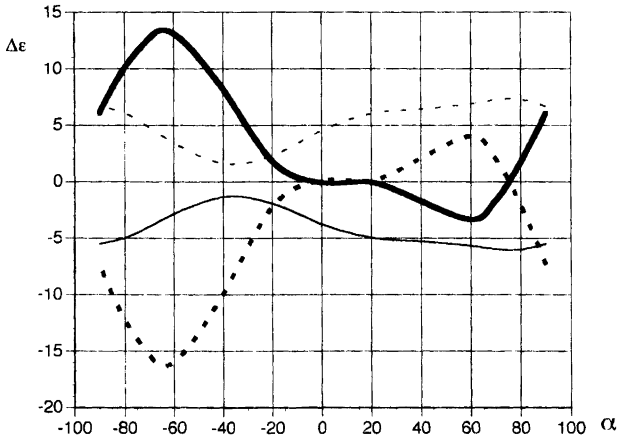


Fig. 8. Δε values calculated for transition 3 as a function of the polarization angle α, assuming the transition moment μ=2.36 D and Δ=15 nm. Solid lines represent the high-energy, broken lines the low-energy transition. Bold lines represent form **A**, normal lines form **B**.

from isomers **A** and **B**. These calculations can also be used as a qualitative model for other π→π* transitions in the thioamide plane. The results (Fig. 8) show that isomer **B** gives positive couplets for all polarization directions. This is because the dihedral angle between identical transitions in the two thioamide chromophores in this isomer is ca. +60° irrespective of the value of α. The variations in couplet strength are due to variations in the projections of the transition moments on a plane perpendicular to an axis between the centra of the chromophores. This makes it impossible to deduce a value for α for transition 3 from these data.

The couplets calculated for isomer **A** show much larger variations in sign and strength. It is worth noting that very weak couplets are predicted for the range α=−10° to +30°, which explains the absence of a couplet for isomer **A** at 275 nm.

The CD spectrum of *R*-**1** appears with opposite signs to that of *R*-**7**, although the two compounds have the same absolute configurations. The predicted conformations differ in the rotation of the acetamido groups (Table 1), but a calculation of the CD spectrum with the geometry predicted for *R*-**1** gives the same sign sequence as for *R*-**7**. The reason for the difference between experimental and calculated spectra may be dimer formation or the presence of conformations other than those predicted by the MM2-91 calculations. Kajtar *et al.*[32] found that the CD spectrum of (*R*)-3-methyl-2-pyrrolidinethione is profoundly influenced by dimer formation. This effect was not significant in acetonitrile solution, but it is likely that dimers with two hydrogen bonds in compounds **1**, **3** and **5** are stable also in this solvent, as indicated by the NMR spectra. It is clear that the CD spectrum of *R*-**1** is strongly solvent dependent. The spectrum in ethanol displays one band at 199 nm with Δε=+13.7 and one at 221 nm with Δε=−0.49. The UV maximum is shifted from 198 nm in acetonitrile to 193 nm in ethanol, and the shape of the CD spectrum in ethanol indicates that a conformation predominates, in which the exciton mechanism is of importance, giving rise to a positive couplet, but in which the one-electron mechanism is less important than in the conformation predominating in acetonitrile solution.

The CD spectrum of *R*-**3**, with bands at 291 and 265.5 nm, indicates contributions from two forms. The weak negative band at 291 nm is probably a residue of a negative π→π* band, which is partly eliminated by a stronger positive band of the same kind from another conformer. No band corresponding to transition 3 is observed. The spectrum calculated for the MM2-minimized structure shows little similarity with the experimental one.

The conformation predicted for compound **5** differs from that of **11**, the angles θ_1 and θ_2 being ca. 100° and 117°, respectively (Table 2). This leads to considerably different calculated CD spectra (Table 5), but the experimental spectrum of *R*-**5** differs also from the calculated one. The proposed explanation is the same as for *R*-**1**.

Summing up, the analysis of the CD spectra of *R*-**1**, *R*-**3** and *R*-**5** leads to the conclusion that the conformational situation is different from that deduced from the NMR spectra in $CDCl_3$ solution, either due to dimer formation or to the appearance of unpredicted conformations.

Initially it was hoped that it would be possible to derive the absolute configurations of the *cis* compounds **4** and **10** from their CD spectra. The spectrum calculated for the conformer predicted to be dominant for the 1*S*, 2*R* enantiomer of **10** agrees quite well with the experimental spectrum for the first eluted enantiomer (Table 4), but unfortunately the same can be said for the theoretical spectrum of the 1*R*, 2*S* enantiomer of a conformer predicted to be only 1 kJ mol^{-1} higher in energy. Considering the uncertainty in the calculated Δε values and the weakness of the experimental spectrum, it is inadvisable to make an assignment of the absolute configuration of **10** based on a comparison of the experimental and theoretical CD spectra.

The CD spectra calculated for the 1*S*, 2*R* configurations of the two conformations of **4** predicted to be most stable by the MM2-91 calculations are quite different from the experimental spectrum, and no conclusion about the absolute configuration can be drawn.

Conclusion

In previous works[1–3] the prevalence of *Z*,*Z* isomers of *N*,*N*'-dimethyl-1,2-bis(thioacetamido)ethanes has in part been rationalized by a preference for *gauche* forms, in which an energetically particularly favourable conformation with antiparallel C=X groups equivalent to form **A** is possible. In compounds **1**–**12** only *gauche* forms exist perforce (assuming diequatorial *trans* isomers), and we find a strong predominance of *Z*,*Z* isomers for all NH compounds and a somewhat less clear and solvent-dependent predominance of these isomers for the *trans*

N,N'-dimethyl compounds. However, the *cis N,N'*-dimethyl compounds prefer to exist as *Z*(eq), *E*(ax) isomers with *Z,Z*, *E,E* and *Z*(ax), *E*(eq) isomers quite close in energy. The isomers derived from the *trans N,N'*-dimethyl compounds from force-field calculations and analysis of NMR spectra are strongly supported by the analysis of the CD spectra, whereas the information obtained from the CD spectra of the NH compounds is less valuable, possibly due to formation of hydrogen-bonded complexes. The CD spectra of the *cis* monothio compounds **4** and **10** could not be analysed because of the conformational diversity of these compounds.

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