Conformational analysis of (*R*,*R*)- and (*R*,*S*)-*N*,*N*-bis-(1-phenylethyl)-acetamide and -thioacetamide. A study by NMR spectroscopy and by empirical force-field and AM1 calculations

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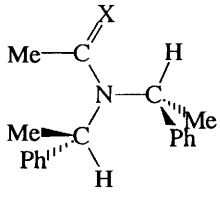
The static and dynamic stereochemistry of the diastereoisomeric (*R*,*S*)- and (*R*,*R*)-*N*,*N*-bis-(1-phenylethyl)acetamides and their thio analogues has been studied by ^{1}H NMR spectroscopy and by the MM2 and AM1 methods. Assignment of the methyl and methine proton resonances was performed by a 2D-NOESY study, which also gave information about exchange processes. Two different processes were identified, the normal (thio) amide rotation leading to exchange of the *E* and *Z* 1-phenylethyl groups and a process with lower energy barrier exchanging two rotamers differing in the orientation of the 1-phenylethyl groups. Rate constants and free energy barriers for these processes were determined by bandshape analysis. The rotamers were identified with the aid of the chemical shifts and by AM1 and empirical force-field calculations and the interconversion trajectories were studied by the same theoretical methods. Barrier differences between the *R*,*S* and *R*,*R* diastereoisomers were qualitatively reproduced by the AM1 calculations.

The MM2 calculations utilizing the dipole–dipole interaction scheme were shown to exaggerate the stabilities of conformers with the *Z* phenyl group turned towards the (thio) carbonyl group. Better agreement with experiments was obtained when monopolar charge interactions were used, but the results were found to depend critically on the choice of the charges.

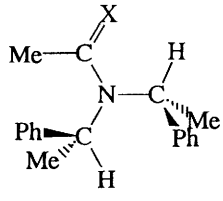
Introduction

The stereochemistry of *N*,*N*-disubstituted amides and thioamides has been the subject of considerable interest over the years, partly because of the relation between amides and peptides and partly because the amide framework has convenient dimensions for notable steric interactions and strong magnetic anisotropy to facilitate NMR studies. Previous studies of *N*,*N*-diisopropylamides, -thioamides and -selenoamides have shown that the isopropyl groups take up more or less bisected arrangements with respect to the amide plane and that in general four different minimum energy conformations are feasible.[1] The conformations of compounds containing chiral secondary groups such as 1-phenylethyl and 1-methoxycarbonylethyl attached to planar heteroaromatic rings have been studied, and also in these cases bisected conformations have been demonstrated.[2–5]

The purpose of the investigation presented here is to study interactions between two chiral secondary groups, in one case with the same and in the other with opposite chiralities. We have chosen (*R*,*S*)- and (*R*,*R*)-*N*,*N*-bis(1-phenylethyl) acetamide (**1a** and **2a**) and their thio analogues (**1b** and **2b**) as models. Similar compounds have previously been studied by Raban and co-workers, although with different purposes. The 2,4-dinitrobenzenesulfenyl derivatives of (*R**,*R**)- and (*R*,*S*)-*N*,*N*-bis(1-phenylethyl) amine were studied as examples of axial pseudo-asymmetry[6] and the α-methoxyphenylacetyl derivatives of the same amines were studied to elucidate the general stereochemical relations in systems containing three asymmetric centres.[7] Both studies gave rise to methods to distinguish between (*R**,*R**)- and (*R*,*S*)-*N*,*N*-bis(1-phenylethyl) amine, but the detailed conformations of the 1-phenylethyl groups were not studied.



1 (*R*,*S*)



2 (*R*,*R*)

a, X = O

b, X = S

Experimental

Materials

A mixture of (*R*,*R*)- and (*R*,*S*)-*N*,*N*-bis(1-phenylethyl)amine was prepared by reduction of the acetophenone Schiff base of (*R*)-1-phenylethylamine according to Overberger *et al.*[8] Reaction of this mixture with acetic anhydride gave a mixture of the corresponding acetamides, which were separated by air-pressure driven column chromatography on silica (Merck 60 mesh) with a 3:8 (v/v) mixture of ethyl acetate and light petroleum (bp 60–70 °C) as the mobile phase. Thionation of **1a** and **2a** to the corresponding thioacetamides was performed by reaction with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide ('the Lawesson reagent') by the standard technique for preparing thioamides.[9] Both acetamides and thioacetamides were purified by recrystalliz-

Table 1 ^{1}H NMR data for compounds **1a**, **2a**, **1b** and **2b**

Compound/Solvent	T/K	p[a]	Major rotamer					Minor rotamer				
			Z-CH	E-CH	Z-CH_3	E-CH_3	CH_3CO/S	Z-CH	E-CH	Z-CH_3	E-CH_3	CH_3CO/S
1a/[$^2H_8$]toluene	190	0.72	6.82	3.97	1.07	0.65	1.55	3.71	4.15	*ca.* 1.5	0.88	1.80
2a/[$^2H_8$]toluene	190	0.64	7.02	4.26	1.06	*ca.* 1.1	1.49	3.83	4.26	1.90	0.87	1.74
2a/CD_2Cl_2	190	0.60[b]	4.18	5.26	1.73	1.73	2.36	6.43	4.57	1.60	1.60	1.58
1b/[$^2H_8$]toluene	300	0.985	7.93	4.56	1.31	0.89	2.27					
1b/$CDCl_3$	300	0.988	7.71	4.92	1.67	1.19	2.38	4.80[c]	5.75[c]			
2b/[$^2H_8$]toluene	300	0.985	8.01	4.67	1.29	1.29	2.24					
2b/$CDCl_3$	300	0.988	7.62	5.08	1.72	1.85	2.33	5.02[c]	5.76[c]			

[a] Fractional population of major rotamer. [b] Major and minor rotamer exchanged compared with [$^2H_8$]toluene. [c] Observable in NOESY.

Table 2 Rate constants (k/s^{-1}) and free energy barriers ($\Delta G^{\ddagger}$/kcal mol^{-1})[a] for rotations in compounds **1a**, **2a**, **1b** and **2b**

Compound/Solvent	T/K	k/s^{-1}	$\Delta G_{major \rightarrow minor}$/kcal mol^{-1}	T/K	k/s^{-1}	$\Delta G^{\ddagger}_{E \rightarrow Z}$/kcal mol^{-1}
1a/[$^2H_8$]toluene	217	75	10.7 ± 0.1	291	115	14.3 ± 0.1
	207	27	10.6 ± 0.1			
1a/CD_2Cl_2	207	85	10.1 ± 0.1			*b*
2a/[$^2H_8$]toluene	198	48	9.9 ± 0.1	291	98	14.4 ± 0.1
2a/CD_2Cl_2	206	197	9.7 ± 0.1			*b*
1b/[$^2H_8$]toluene	296	121	14.5 ± 0.1	365	165	17.8 ± 0.1
1b/$CDCl_3$	295	124	14.4 ± 0.1			
2b/[$^2H_8$]toluene	300	121	13.7 ± 0.1			*b*
2b/$CDCl_3$	280	126	13.7 ± 0.1			

[a] 1 cal = 4.184 J. [b] Too small shift difference.

ation from hexane. (*R,S*)-*N,N*-Bis(1-phenylethyl)acetamide **1a**, colourless crystals, mp 100–101 °C [*m/z* observed 268.1702 (M^+ + 1), calc. for $C_{18}H_{22}NO$ 268.1701]. (*R,R*)-*N,N*-Bis(1-phenylethyl)acetamide **2a** colourless crystals, mp 88–89 °C [*m/z* observed 268.1708 (M^+ + 1), calc. for $C_{18}H_{22}NO$ 268.1701]. (*R,S*)-*N,N*-Bis(1-phenylethyl)thioacetamide **1b**, colourless crystals, mp 123–124 °C [*m/z* observed 283.1388 (M^+), calc. for $C_{18}H_{21}NS$ 283.1395]. (*R,R*)-*N,N*-Bis(1-phenylethyl)thioacetamide **2b**, colourless crystals, mp 147–148 °C [*m/z* observed 283.1399 (M^+), calc. for $C_{18}H_{21}NS$ 283.1395].

Intruments and measurements

All NMR spectra were recorded with a Bruker Model AC 250 NMR spectrometer equipped with a BVT-100 variable temperature controller. The samples were all 0.1 mol dm^{-3} except for those used in the 2D-NOESY experiments, which were *ca.* 0.5 mol dm^{-3}. The temperatures were measured with the aid of a methanol NMR thermometer [10] as a capillary insert in the sample tube. In rare cases of overlap between signals of interest and methanol signals the temperature controller display was used in conjunction with a calibration curve, made from several runs with the methanol insert. Temperatures measured in this way were shown to be precise to within 1 K with respect to the direct reference.

The phase-sensitive 2D-NOESY and EXSY spectra were obtained with the Bruker NOESYPH.AU pulse program. The spectra were collected overnight by 256 '64 scans' experiments (increment) in 512 data points with a sweep width of 2100 Hz. The 256 × 512 data points were Fourier-transformed with a sine bell apodization in both dimensions. By use of a mixing time close to T_1 in a standard phase-sensitive 2D-NOESY pulse sequence, combined exchange and NOE correlated spectra were obtained. From these spectra the total exchange pattern (negative NOE) and conformational information (positive 'real' NOE) could be deduced.[11] Since the *Z* methine proton resonances in the major forms could be unequivocally assigned (*vide infra*), a total assignment of resonances was possible (Table 1). However, attempts to obtain clear positive NOEs for the acetamides **1a** and **2a** failed, probably because of lack of long-term temperature stability and the general difficulty of recording high-quality spectra at low temperatures (180–190 K).

The rate constants for the exchange processes were evaluated by iterative least-squares fitting of simulated exchange-broadened NMR spectra to the experimental spectra with the DNMR5 program.[12,13] T_2 values were obtained from spectra of acetamides at a low exchange rate and owing to the large chemical shift differences involved, possible errors in T_2 have no significant influence on the rate constants. The only source of error of importance in the calculated free energy barriers is in the temperature measurement. The estimated confidence limits to the free activation energies in Table 2 are based on an assumed maximum temperature error of ± 2 K.

Mass spectra were recorded with a JEOL Model SX-102 mass spectrometer. The thioamides **1b** and **2b** gave M^+ ions of *ca.* 10% abundance with electron ionization, while the M^+ ions of the amides **1a** and **2a** were unobservable in this mode. Instead, chemical ionization with methane was used and gave prominent (*ca.* 90%) (M^+ + 1) peaks.

CD spectra were recorded with a JASCO Model J-500A spectropolarimeter with absolute ethanol as solvent. The variable-temperature CD spectra were recorded with the equipment described earlier.[3]

Theoretical calculations

The empirical force-field calculations were performed with the MacMimic [14] implementation of the Allinger MM2(91) force field,[15,16] or with the closely related MMX force field from the program PCModel.[17,18] The non-standard force-field parameters used have been published previously.[19] MM2 calculations were performed both with the standard dipole–dipole interaction scheme and with dipoles replaced by atomic charges. In MMX, the only charges available are obtained from the bond dipoles. They were found to be unrealistically small.

Energy maps were generated for all compounds and by all methods used at a resolution of 10° on both rotor dihedral angles ω_Z and ω_E. ω_Z and ω_E are the (X=)C–N–C–H dihedral angles in the *Z* and *E* 1-phenylethyl groups (X = O or S). Energy curves for calculated rotational trajectories were extracted from the maps by choosing the lowest energy value for each single dihedral angle of one rotor. Double checks

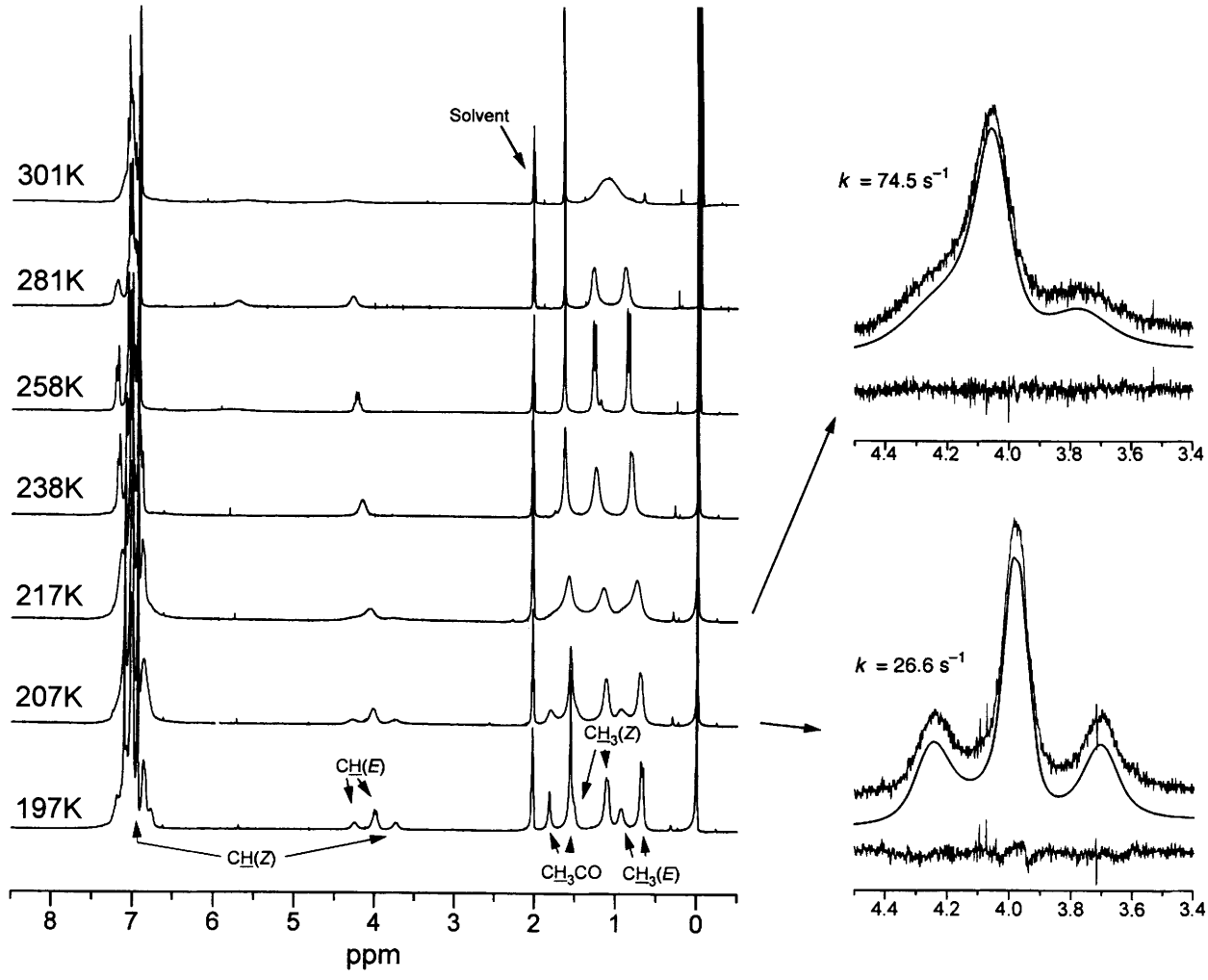


Fig. 1 Temperature-dependent ^1H NMR spectra of **1a** in [$^2H_8$]toluene together with two sets of experimental, simulated and difference spectra of the methine protons in the range δ 3.4–4.5

were made for these data by making clockwise and anti-clockwise rotations around the respective bonds in the areas of interest.

Semi-empirical AM1[20] calculations were performed by the MOPAC (6)[21,22] or HyperChem[23] programs. MOPAC was used for single-point calculations and to obtain optimized geometries (convergence limit = 0.1 kcal mol^{-1} Å^{-1}†). HyperChem proved to be more stable than MOPAC for generating energy surface maps. In contrast to MOPAC's internally fixed coordinates, HyperChem makes use of energy restraints when a dihedral driver is applied. Every point on the energy surface maps was optimized (convergence limit = 0.5 kcal mol^{-1} Å^{-1}) with a restraint value of 200 kcal mol^{-1} Å^{-1} on the dihedral angles and then followed by a single-point calculation without the restraints.

Results and discussion

The ^1H NMR spectrum of **1a** in [$^2H_8$]toluene (Fig. 1, Table 1) recorded in the temperature range 340–180 K showed broadenings as the result of two rate processes. In the higher temperature range a process exchanges methyl and methine protons in the 1-phenylethyl groups, but does not affect the acetyl methyl resonance. This process, which is the normal amide rotation about the N–C(=O) bond (*E*–*Z* exchange) is slow at 258 K, as indicated by the sharp doublet of doublets due to the 1-phenylethyl methyl protons. However, at this temperature one methine resonance was already broadened by an exchange process with lower activation energy, since the corresponding proton exchange takes place between two sites with very different chemical shifts. At successively lower temperatures all resonances broadened and split into two sets in the ratio 0.72:0.28. One of the 1-phenylethyl methyl resonances of the major form appeared unusually shielded (δ 0.65). The effect of the temperature changes on the aromatic proton resonances was small. Below 200 K no further changes occurred. Simulation of the methyl resonances in the temperature range 280–300 K and of the methine resonances in the range 190–220 K gave rate constants from which free activation energies ($\Delta G^{\ddagger}$) for the two processes were calculated (Table 2). They were found to be rather insensitive to the temperature.

A similar study of the ^1H NMR spectrum of the (*R*,*R*)-compound **2a** in [$^2H_8$]toluene (Table 1) gave in general similar results, but some conspicuous differences were noted: the 1-phenylethyl methyl resonances of the major form appeared at normal positions (δ *ca.* 1.1), and the aromatic resonance, which covered a narrow chemical-shift range in the spectrum of **1a**, displayed a high-field and a low-field multiplet well separated from the main resonance at δ *ca.* 7.2. The rotational barrier for the low energy process is lower for the (*R*,*R*) than for the (*R*,*S*) compound (Table 2).

The ^1H NMR spectra of the thioamides **1b** and **2b** in [$^2H_8$]toluene at 320 K showed two sets of sharp 1-phenylethyl resonances corresponding to the *E* and *Z* groups. As expected,[24] the barrier to rotation around the C–N bond is considerably higher for the thioamides than for the amides (17.8 *versus* 14.3 kcal mol^{-1}, Table 2). One of the methine resonances

† 1 kcal = 4.184 kJ.

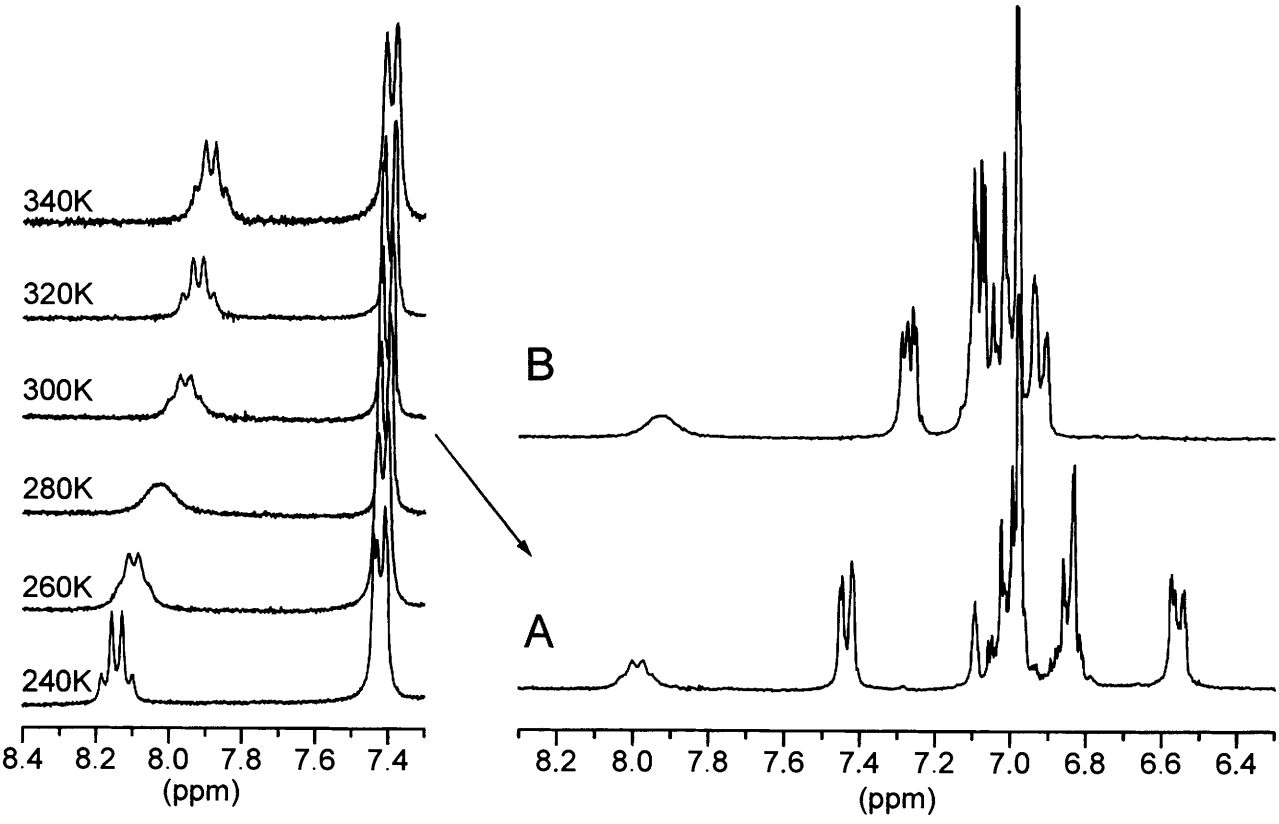


Fig. 2 Temperature-dependent ^{1}H NMR spectra of the low-field methine proton in **2b** (left part) and spectra of the aromatic protons of **2b** (A) and **1b** (B) at 300 K (right part). Solvent [$^2H_8$]toluene.

appeared unusually deshielded for both compounds, δ 7.93 and 8.01 in [$^2H_8$]toluene, 7.71 and 7.62 in [^{2}H]chloroform (Table 1). When the temperature was lowered, this resonance broadened conspicuously, but sharpened again at still lower temperatures (Fig. 2), the maximum broadening occurring at 296 K for **1b** (295 K in [^{2}H]chloroform) and at 280 K for **2b**. The remaining resonances showed no strong temperature dependence. This behaviour is indicative of an exchange process between two components in a strongly biased equilibrium system. The spectrum at slow exchange, at or below 260 K, shows only the resonances of the major form. However, owing to saturation transfer and spin diffusion in the 2D-NOESY experiment, the minor methine proton resonances became observable and their chemical shifts could be determined (Table 1). With these data available, it was possible to determine the rotamer populations and exchange rates[25,26] (Tables 1 and 2) and it was found that the fractional populations of the minor rotamers were as low as 0.012 and 0.015. Also in this case the (*R*,*R*) compound was found to have the lower energy barrier (Table 2). As follows from Table 1 and Fig. 2, the shift characteristics of the major rotamer of **1a**, strongly shielded *E*-methyl protons, and of the major rotamer of **2a**, split aromatic resonances, were also observed for **1b** and **2b**, respectively, which indicates that similar major rotamers are involved in the exchange systems of the amides and the thioamides, although with different populations.

In order to obtain a basis for the analysis of the ^{1}H NMR spectra of **1a** and **2a**, we have calculated the energies of the two structures as a function of the two dihedral angles ω_Z and ω_E describing the rotation of the 1-phenylethyl groups, using an empirical force field method, MM2(91), as well as the semi-empirical AM1 method. The resulting energy maps are similar for the four compounds and display four major energy minima (A–D, Fig. 3) corresponding to those found for *N*,*N*-diisopropylamides and -thioamides[1,27] and with ω_Z and ω_E close to 0 or 180°.

The terms rotamer and conformer are synonymous and signify minimum energy conformations, but for clarity we will in the following use rotamer for (in principle) NMR-identifiable entities and conformer for structures from theoretical calculations. The NMR spectra discussed above indicate that the amides **1a** and **2a** exist as mixtures of two rotamers with rather similar energies (ΔG° = −0.15–+0.36 kcal mol^{-1}), whereas the thioamides **1b** and **2b** display two rotamers with considerably different energies (ΔG° = 2.5 kcal mol^{-1}). It should be remembered that what is here denoted as a rotamer, characterized by one set of NMR resonances, may in fact be a mixture of two or more rotamers, separated by low energy barriers and with an NMR spectrum that is the population-weighted mean of the spectra of the individual species. When in the following we discuss one rotamer, we implicitly imply the major species in such a mixture.

The low-field position (δ 6.82 and 7.02 in [$^2H_8$]toluene) of one methine proton resonance of the major rotamers of **1a** and **2a** clearly assigns these protons to the *Z* 1-phenylethyl group in the B and/or the D form, in which the C–H group is more or less parallel to the C=O group,[28,29] with the proton in the region of strong deshielding by the carbonyl group. Consequently, the minor rotamer in toluene solution is assigned to the A and/or the C conformer. In the B conformer of **1a**, the *E* methyl group falls in the shielding region of the *Z* phenyl group, and therefore this form is the best candidate for the major rotamer of **1a** with the *E* methyl resonance at δ 0.65. In the D conformer, the *E* methyl and *Z* phenyl groups are too distant to give significant shielding effects. In the spectrum of **2a**, on the other hand, the methyl resonances have normal chemical shifts, whereas one group of aromatic proton resonances falls at unusually high field (δ *ca.* 6.5) and another one at low field (δ *ca.* 7.4). This is also in agreement with the nearly orthogonal orientation of the phenyl groups in the B (but not in the D) conformer, with the *Z* phenyl group shelding and the *E* phenyl group deshielding the neighbouring phenyl group (see Fig. 4). Similar effects were reported for the NMR spectra of the (*R**,*R**) form of *N*,*N*-bis(1-phenylethyl)-α-methoxyphenylacetamide,[7] but in this case

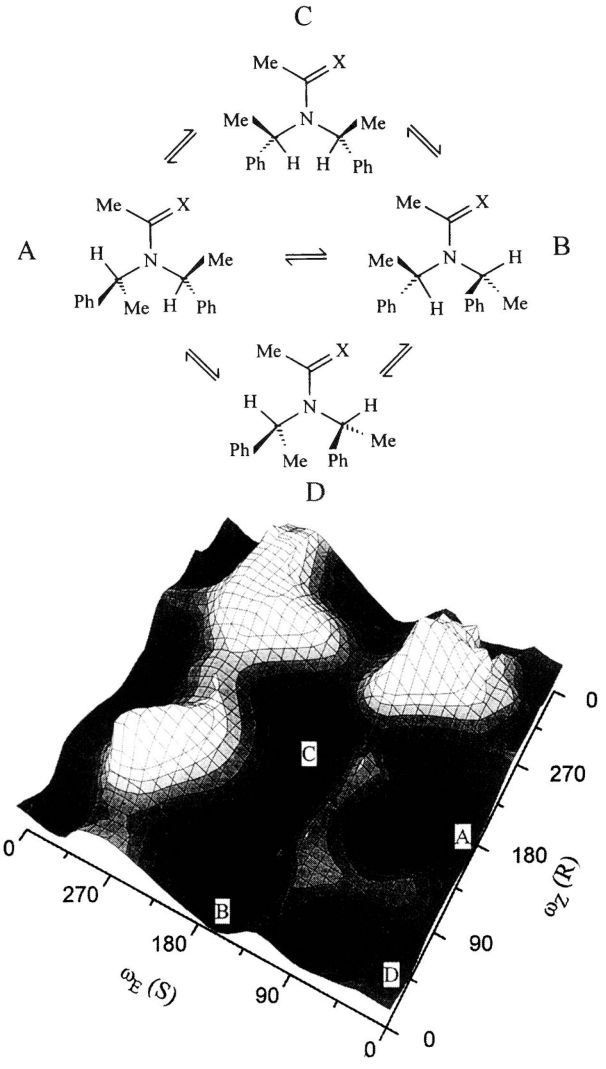


Fig. 3 Exchange scheme for **1a** (X = O) and **1b** (X = S) together with the MM2 potential energy map for **1a** produced by stepwise rotation of the two dihedral angles ω_Z and ω_E. Energy equidistance = 1.0 kcal mol^{-1}.

the splitting was ascribed to shielding/deshielding by the aromatic ring in the acyl group.

The spectra of the minor rotamers of **1a** and **2a** in [$^2H_8$]toluene show *Z* methine resonances at unusually high field. This agrees with the A conformer, where shielding by the *E* phenyl group is expected, but not with the C conformer. Thus conformer A is expected to dominate in the minor rotamer. These arguments are equally valid for **1a** and **2a**. Further support for this assignment is obtained from the solvent effect on the chemical shifts. In Table 2, spectra are reported for **2a** both in [$^2H_8$]toluene and in [$^2H_2$]dichloromethane. There is a shift in the bias of the equilibrium, the major form in [$^2H_8$]toluene becoming the minor one in [$^2H_2$]dichloromethane. The most notable solvent effect on the chemical shifts is for the *E* methine proton, which appears at δ 4.26 in [$^2H_8$]toluene and at 5.26 in [$^2H_2$]dichloromethane. This is in harmony with conformer A being the minor one in [$^2H_8$]toluene, since it is generally accepted that aromatic molecules solvate and shield preferentially the regions of a dipolar solute molecule, which are most distant from the negative pole, while protons near the negative pole are deshielded.[30]

The major rotamers of the thioamides **1b** and **2b** display even more deshielded *Z* methine protons (δ 7.93 and 8.01 in [$^2H_8$]toluene, 7.71 and 7.62 in [$^2H_2$]dichloromethane, Table 1), leaving conformers B and D as the only alternatives for these rotamers. The same pattern of chemical shifts as observed for

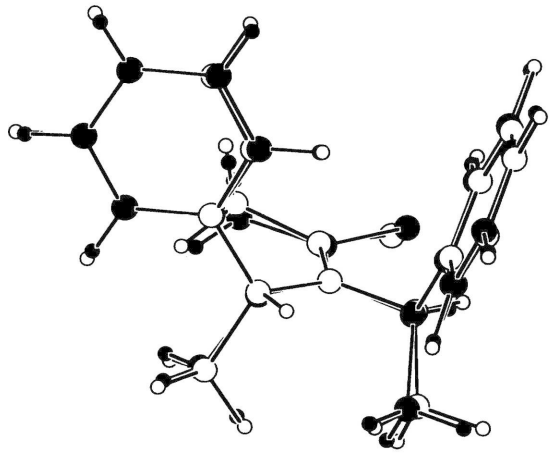


Fig. 4 Overlay of the crystal structure of **2b** (dark atoms) and the MM2 conformation B of **2b** minimized with AM1 charges. RMS of the differences for all non-hydrogen atoms = 0.15 Å.

the acetamides, with shielded *Z* methyl group for the (*R*,*S*) and spread-out aromatic proton resonances for the (*R*,*R*) compound lead to the conclusion that the most stable conformer in both thioamides is B. This assignment is further supported by the NOESY results (Table 3). When the observed appearances of NOE enhancements are correlated with interproton distances obtained from the conformers energy-optimized with the AM1 method (*vide infra*) it appears that the distances related to NOE enhancements fall in the quite realistic range 2.2–2.8 Å for conformer B of **1b** (*R*,*S*) and 2.1–2.7 Å for the same conformer of **2b** (*R*,*R*). For all other conformations much wider and less realistic ranges of distances are observed with the exception of the A conformer of **1b**, which shows an acceptable range of distances (2.2–3.1 Å). However, this conformer has already been excluded by other arguments. A recent X-ray crystallographic study of **2b**[31] (Fig. 4) shows that this compound exists as the B conformer in the solid state.

For the minor rotamers of **1b** and **2b** insufficient chemical shift data are available to allow a decision about which of conformers A or C is the best representation.

The relative conformational energies calculated for the four conformers A–D of compounds **1a**–**2b** are shown in Table 4 together with experimental data for [$^2H_8$]toluene solution. It is obvious that the empirical force-field calculations with MM2 using the dipole–dipole interaction model and MMX with the point charge model seriously overestimate the energy of the B conformer, or perhaps rather underestimate the energy of the A conformer. In the default version of MM2(91) the C–H dipoles are neglected. However, inclusion of these dipoles does not significantly change the relative energies of the four conformers. On the other hand, the AM1 calculations, except for the direct optimization of **1a**, predict the B conformer to have the lowest energy, in agreement with experiments. A similar problem with MM calculations giving too low energy to A type conformers was encountered in a study of *N*-1-phenylethyl-Δ^4-1,3-thiazoline-2-thiones.[3] This discrepancy may be due to an underestimation by the dipole–dipole interaction model of the repulsion between the strongly negative carbonyl oxygen and thiocarbonyl sulfur atoms on one side and the negative phenyl carbon atoms on the other, since these atoms approach one another rather closely in the A conformer. We have used the MM2(91) option to introduce point charge interactions instead of dipole–dipole interactions. The point charges were taken from AM1 calculations (Table 5), and this led to an inversion of the relation between the A and B conformer energies for **1a**, **1b** and **2a**, but for **2b** the D conformer was predicted to be 1.3 kcal mol^{-1} lower in energy than the B conformer. The AM1 charges in the aryl and alkyl groups seem quite realistic and correspond reasonably well to

Table 3 Correlation scheme between observed positive NOEs (bold) and distances (Å) measured on the AM1 optimized models of **1b** and **2b**

1b

A

^{1}H	*Z*-*o*-Ph	*E*-*o*-Ph	*Z*-CH	*E*-CH	*Z*-CH_3	*E*-CH_3	CH_3CS
Z-*o*-Ph		4.3	2.6	4.2	**2.3**	**2.4**	5.1
E-*o*-Ph	4.3		2.6	2.4	**3.1**	**2.2**	2.7
Z-CH	2.6	3.9		3.6	**2.5**	2.3	4.9
E-CH	4.2	2.9	3.7		**2.4**	**2.4**	2.2
Z-CH_3	**2.2**	**2.4**	**2.4**	**2.4**		4.4	4.6
E-CH_3	**2.8**	**2.2**	3.9	**2.5**	4.3		**2.7**
CH_3CS	4.2	3.3	4.5	3.8	4.5	**2.2**	

B

C

^{1}H	*Z*-*o*-Ph	*E*-*o*-Ph	*Z*-CH	*E*-CH	*Z*-CH_3	*E*-CH_3	CH_3CS
Z-*o*-Ph		2.2	2.7	2.7	**2.2**	**5.4**	5.7
E-*o*-Ph	3.1		2.8	2.5	**4.8**	**2.5**	2.4
Z-CH	2.6	4.6		2.2	**2.4**	3.6	4.8
E-CH	4.1	2.4	4.3		**2.8**	**2.4**	4.0
Z-CH_3	**3.6**	**3.8**	**2.4**	**4.3**		2.2	4.5
E-CH_3	**4.3**	**2.2**	4.1	**2.4**	2.5		**2.1**
CH_3CS	3.9	3.2	4.5	2.1	4.6	**2.3**	

D

2b

A

^{1}H	*Z*-*o*-Ph	*E*-*o*-Ph	*Z*-CH	*E*-CH	*Z*-CH_3	*E*-CH_3	CH_3CS
Z-*o*-Ph		3.2	2.7	**4.0**	**2.4**	4.7	5.6
E-*o*-Ph	3.1		2.6	**2.4**	4.0	**2.2**	2.3
Z-CH	2.4	4.1		3.7	**2.4**	2.5	4.9
E-CH	**2.5**	**2.7**	3.7		**4.2**	**2.4**	2.1
Z-CH_3	**2.2**	4.5	**2.4**	**2.4**		2.3	4.3
E-CH_3	5.8	**2.3**	4.0	**2.5**	2.4		**2.9**
CH_3CS	4.1	2.7	4.6	3.8	4.8	**2.1**	

B

C

^{1}H	*Z*-*o*-Ph	*E*-*o*-Ph	*Z*-CH	*E*-CH	*Z*-CH_3	*E*-CH_3	CH_3CS
Z-*o*-Ph		2.4	2.7	**3.8**	**2.3**	2.2	5.2
E-*o*-Ph	3.6		3.7	**2.6**	2.3	**2.3**	2.7
Z-CH	2.6	4.3		2.2	**2.5**	2.6	4.8
E-CH	**4.4**	**2.6**	4.3		**2.7**	**2.4**	3.8
Z-CH_3	**2.3**	2.9	**2.3**	**4.1**		4.5	4.4
E-CH_3	3.0	**2.4**	4.0	**2.4**	3.0		**2.2**
CH_3CS	3.9	2.6	4.5	2.1	5.3	**2.9**	

D

Table 4 Calculated relative conformational energies (kcal mol^{-1}) for compounds **1a**, **2a**, **1b** and **2b**

Compound	Conformation	MM2(87/91) (default)	MM2(87/91) (AM1 charges)	AM1 single point (MM2 geometry)	AM1 optimized (MOPAC 6)	MMX (PC Model)	Experimental[a]
1a	A	0.00	2.07	1.35	0.00	0.00	0.36
	B	1.41	0.00	0.00	0.33	0.75	0.00
	C	2.79	2.77	3.00	1.48	1.37	
	D	0.22	1.99	5.50	3.27	3.84	
2a	A	0.00	0.77	1.21	1.03	4.67	0.22
	B	1.42	0.00	0.00	0.00	1.37	0.00
	C	1.85	2.12	5.09	1.61	0.00	
	D	1.65	0.37	2.70	2.14	2.17	
1b	A	0.00	1.06	4.83	1.44	0.00	2.49
	B	1.17	0.00	0.00	0.00	0.75	0.00
	C	3.09	5.78	8.62	3.27	1.37	
	D	0.43	1.53	9.06	3.37	3.84	
2b	A	0.00	4.91	1.94	2.44	0.67	2.49
	B	1.01	1.31	0.00	0.00	1.31	0.00
	C	1.55	2.26	4.81	3.69	0.00	
	D	1.22	0.00	3.50	2.43	2.26	

[a] From [$^2H_8$]toluene. The minor form is assumed to have conformation A.

the generally accepted C–H bond dipole moments. The charge on the thiocarbonyl sulfur atom was predicted by AM1 calculations to be less negative than that for carbonyl oxygen. This is against the general view that thioamides are more strongly polarized than amides, as reflected in higher rotational barriers[24] and dipole moments[32] for thioamides. However, the AM1 charges for *N*,*N*-dimethylacetamide and its thio analogue, with $q(O) = -0.373$ and $q(S) = -0.234$, reproduce quite well the experimental dipole moments (experimental values 3.74 and 4.76 D,[32] calculated values 3.57 and 4.91 D). The unexpectedly high energy of the B conformer of **1b** can be traced to the strongly negative charge on the acetyl methyl carbon atom, which gives strongly repulsive C–C interactions in conformers B and C with ω_E close to 180°. This leads to a relatively lower energy of the D conformer in **2b** with favourable phenyl–methyl interactions but not in **1b** with repulsive phenyl–phenyl

Table 5 Atomic charges from AM1 calculations on model fragments of compounds **1a–2b**, used in MM2 calculations with the point charge option

Atom	Acetamide	Thioacetamide
Oxygen/sulfur	−0.36	−0.24
Carbonyl carbon	0.31	0.04
Nitrogen	−0.33	−0.26
Acetyl methyl carbon	−0.24	−0.24
Acetyl methyl protons	0.10	0.10
Methine carbon	0.08	0.08
Methine proton	0.09	0.13
Phenyl carbon (*ipso*)	−0.11	−0.11
Phenyl carbon (*o*, *m*, *p*)	−0.13	−0.13
Phenyl protons	0.13	0.13
Methyl carbon	−0.20	−0.20
Methyl protons	0.10	0.10

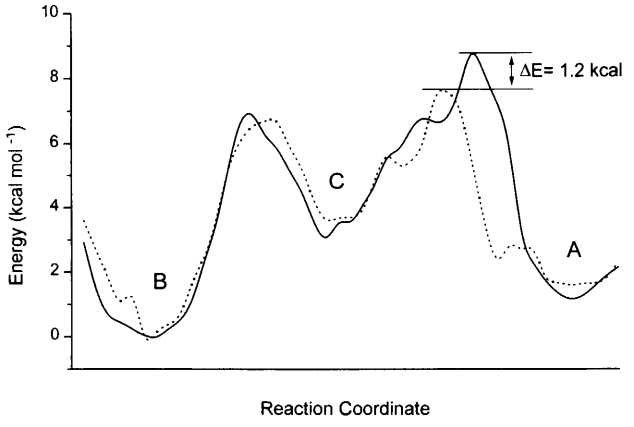


Fig. 5 Potential energy curves along the reaction coordinate (AM1) for the B→A interconversion of **1b** (——) and **2b** (. . .)

interactions. Although we have no indications about the correctness of the high negative charge on the acetyl methyl carbon, it is worth noting that a recent *ab initio* study of (*Z*)- and (*E*)-*N*-methylacetamide[33] predicts charges of *ca.* −0.5 for this carbon atom. It is hardly meaningful to try to modify this charge to obtain better agreement with experiments. At present we are satisfied at having demonstrated that the dipole approximation does not account satisfactorily for the electrostatic contribution to conformational energies when close-lying strongly polar groups are involved.

We have also investigated charge distributions from CNDO and CNDO/S calculations, but the charges obtained for alkyl and aryl carbon and hydrogen atoms were unrealistically low, although the total dipole moments were of the correct order of magnitude. When these charges were used in the MM2 calculations, the energies of the A conformers of **1b** and **2b** were also underestimated.

The geometries of the conformers are probably better reproduced than the energies, as follows from the close similarity between the calculated geometry for the B conformer of **2b** (MMX) and the crystal structure of this compound (Fig. 4).

In early studies of *N*,*N*-diisopropyl-amides and -thioamides it was assumed that the two isopropyl groups perform concerted rotations to interconvert between conformers A and B, but it was later[1,27] shown that these processes are in fact stepwise, proceeding with conformer C and/or D as intermediates. In order to obtain information about the pathways of interconversion for **1** and **2**, we have extracted potential energy curves along the reaction coordinate from energy surface maps. As an example, the curves for **1b** and **2b** are shown in Fig. 5. It appears that the lowest energy interconversion pathway from B to A involves first rotation of the *Z* 1-phenylethyl group to give C as a high energy intermediate, followed by rotation of the *E* group to give A. In this case, the rotation of the *E* group is the rate-determining step and the experimentally observed barrier

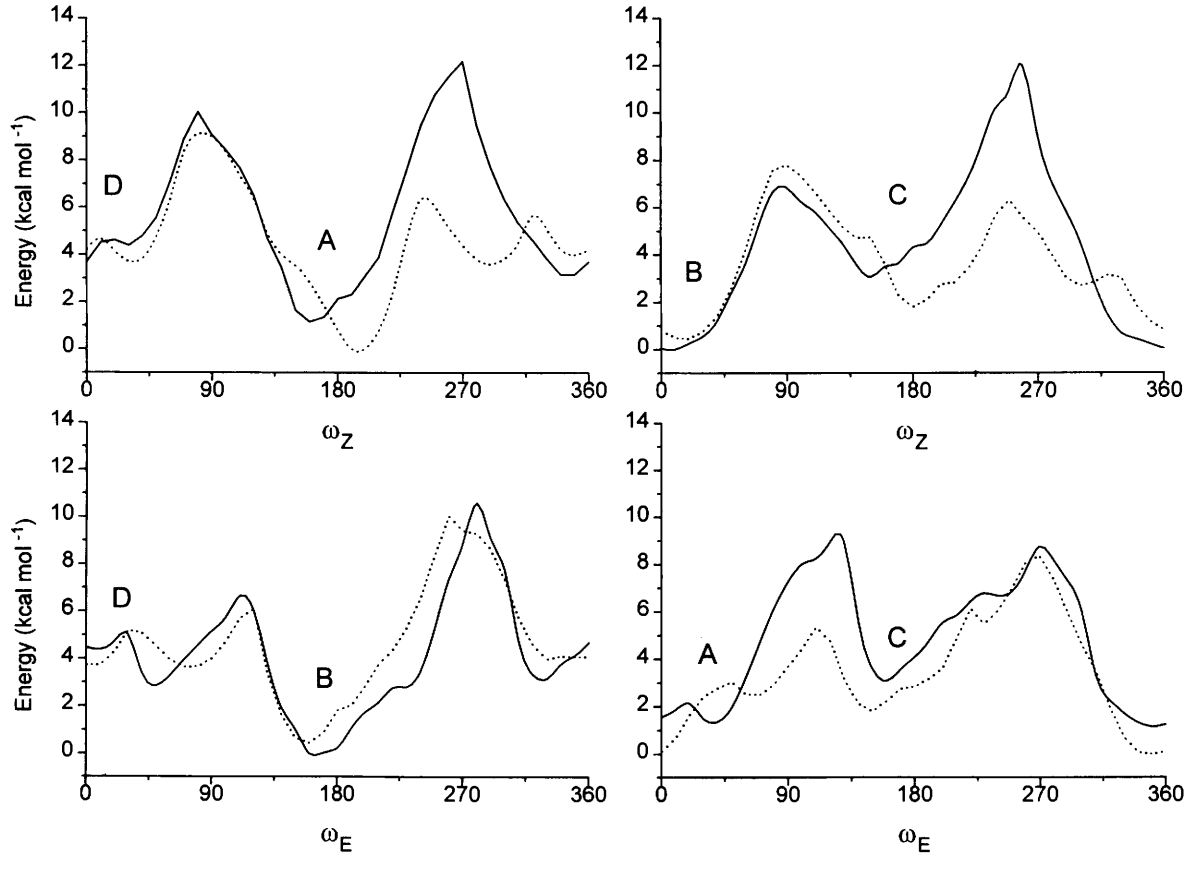


Fig. 6 Comparison of the potential energy curves for the four interconversion pathways of **1b** calculated by AM1 (——) and MMX (. . .)

Table 6 CD spectra of **2a** and **2b** in ethanol

Compound	Temp °C	λ/nm ($\Delta\varepsilon$/dm^3 mol^{-1} cm^{-1})
2a	25	222 (+7.9), 199 (+21.6)
	−80[a]	222 (+8.0), [b]
2b	25	362 (+2.0), 285 (+21.1)
	−78[a]	362 (+2.2), 283 (+32.3)

[a] Corrected for contraction.[35] [b] Too high absorbance.

difference between the (*R*,*S*) and (*R*,*R*) diastereoisomers is qualitatively reproduced by the calculations. Generally, the calculated barriers are somewhat lower than the experimental ones, which is not unusual for the AM1 method.[34]

A comparison of the rotational energy curves obtained for **1b** by the MMX and AM1 methods (Fig. 6) clearly demonstrates the underestimation of the non-bonded repulsive interactions between phenyl and (thio)carbonyl groups. While the energy curves depicting the rotation of the *Z* 1-phenylethyl group from D to A to D and from B to C to B in most cases are remarkably similar considering the different methods when ω_Z is in the range 0–180°, the MMX curve drops considerably below the AM1 curve when ω_Z is in the range 200–300°, the region where the phenyl group passes the thiocarbonyl group.

Compounds **2a** and **2b** are chiral and their CD spectra have been recorded in ethanol solution, at ambient temperature and at temperatures down to *ca.* −80 °C (Table 6). Both compounds display two positive bands in the wavelength region above 195 nm. At shorter wavelengths the UV absorption is too strong to allow recording of the apparently quite weak CD absorption. The band at 222 nm in the spectrum of **2a** can probably be interpreted as being due to the ^1L_a transitions in the benzene chromophores,[36] and the 199 nm band to the $\pi\rightarrow\pi^*$ transition of the amide chromophore.[37] No amide $n\rightarrow\pi^*$ band could be observed. The band at 362 nm in the spectrum of **2b** is undoubtedly the expected thioamide $n\rightarrow\pi^*$ band,[38] while the 285 nm band is ascribed to the thioamide $\pi\rightarrow\pi^*$ transition.[39]

The 222 nm band in the CD spectrum of **2a** changed very little when the temperature was lowered to −80 °C. The same is true for the $n\rightarrow\pi^*$ band of **2b**, whereas the 283 nm band showed a *ca.* 50% increase in intensity. Calculations of the CD spectra of the four minimum-energy conformations of **2b** by the matrix method of Schellman and co-workers[40] using parameters described earlier[41] and geometries from the force-field calculations predict positive $n\rightarrow\pi^*$ and $\pi\rightarrow\pi^*$ bands for all four conformers, in agreement with experiments. In previous work, valuable conformational information about chiral compounds existing as mixtures of two conformers has been obtained from the variation of their CD spectra with the temperature.[42] However, in the case of **2a** and **2b** this variation was not sufficiently distinct to allow conclusions about the dominant conformers.

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