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Conformational Analysis of Crowded Anilides and Thioanilides. The "En-Face" Steric Effect of Aryl Groups

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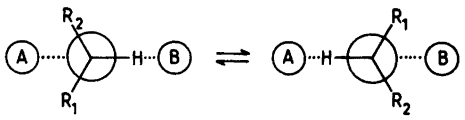
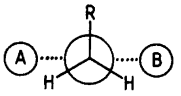
In order to study the interaction of isobutyl, neopentyl, and isopropyl groups with the "face" of aromatic rings, a series of *o,o'*-disubstituted anilides and thioanilides with the above-mentioned groups as *N*-substituents has been investigated by temperature-dependent NMR spectroscopy and by molecular mechanics calculations. The barriers to (thio)acyl group rotation were determined by bandshape and in one case also by stereomutation technique and were found in the range 86–104 kJ mol^{-1}. The barriers to aryl group rotation were studied in 2-chloro-6-methyl-(thio)anilides and were found to be at least 110 kJ mol^{-1}, thus permitting resolution in enantiomers.

The barriers to rotation of the *N*-alkyl groups were too low to be measured by NMR. Molecular mechanics calculations gave the preferred conformations of the neopentyl and isopropyl groups, and the results indicate that the aromatic ring face presents a very small hindrance to the rotation of these groups. The calculated *N*-alkyl group conformations are supported by a comparison of experimental shieldings with those calculated by the ring current model for the magnetic anisotropy of the aromatic ring.

In previous studies from this and associated groups, the conformations and barriers to rotation of primary[1–4] and secondary[5–7] alkyl groups attached to sp^2 hybridized frameworks have been studied by NMR bandshape technique and by empirical strain energy calculations. The alkyl groups have been placed between flanking groups, in which the main interaction either comes from one single atom (O, S, Se in C=O, C=S, C=Se, CH_3O, CH_3S or CH_3Se), or from a group of atoms (CH_3 or other alkyl groups). It



1a *1b*



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has been found in all these cases (see also[8–10]) that secondary alkyl groups in general take up an orientation with the methine proton in or nearly in the sp^2 plane (*1*, parallel orientation[9]), whereas primary alkyl groups ($-CH_2R$) orient themselves with the C–R bond in a plane nearly perpendicular to the sp^2 plane (*2*).

With secondary alkyl groups and unequal flanking groups A and B, two rotamers, *1a* and *1b*, are possible. The equilibrium constants, $K=[1b]/[1a]$, as well as the barriers to interconversion ($\Delta H^{\ddagger}$ or $\Delta G^{\ddagger}$) reflect the steric effects of A and B and can, with due circumspection,[3,4] be used to assess the relative sizes of substituent groups.

This study is part of a series intended to investigate the stereochemical behaviour and apparent size of an aromatic ring as a flanking group. The compounds studied are of the general type *3*.

In these, three kinds of rotational processes are feasible, *viz.*

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(1) rotation around the RCX–N bond (amide/thioamide rotation),
(2) rotation around the N–CHR_1R_2 bond, and
(3) rotation around the N–Ar bond.

The aim of this study is to find the minimum energy conformations, their populations and the barriers separating them with respect to these three rotational processes. For this purpose we have used NMR spectra and empirical strain energy (MMP1)[11,12] calculations.

It is evident that the part of the barrier to torsion around the N–Ar bond, which is due to conjugation, must be quite small, considerably less than the 23.9 kJ mol^{-1} found for aniline.[13] Therefore the aromatic ring must be readily rotated to respond to the steric requirements of the neighbouring groups. In order to have a reasonably well defined orientation of this ring perpendicular to the (thio)amide plane, 2,6-disubstituted aromatic rings were employed. In this way, the other groups will approach the aromatic ring from the planar side ("en face"), *i.e.* its steric effect will be determined by its π-electron cloud.

EXPERIMENTAL

Syntheses. All compounds of type *3* used in this study are found in Table 1 together with the thermodynamic data for the $E \rightarrow Z$ conversion. The anilides were prepared by conventional methods. Most thioanilides were prepared by refluxing the corresponding anilides with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphethane-2,4-disulfide ("the Lawesson reagent")[14] in toluene (method A). However, this method did not work with some hindered anilides, but in these cases thiation was achieved by reaction with diboron trisulfide, prepared *in situ* from bis(tricyclohexyltin) sulfide and boron trichloride according to Steliou and Mrani[15] (method B).

In all cases the final products were purified by preparative TLC (PTLC) on silica gel (Merck 60 F_{254}) with chloroform as solvent, or by preparative GLC (PGC), using 15 % OV-101, 45–60 mesh, in a 3 m column. The purity and identity of the compounds were assessed by ^1H NMR and mass spectra. The ^1H chemical shifts are found with assignment in Table 2.

N-*Neopentyl-2,6-dimethylacetanilide* (*4*). 2,6-Dimethylaniline (12.1 g, 0.10 mol) was added in portions to a stirred solution of pivaloyl chloride (6.0 g, 0.05 mol) in toluene (70 ml) at ambient temperature. After standing at ambient temperature for 1 h, the mixture was refluxed for 5 h, filtered and evaporated to give crude *2,6-dimethylpivalanilide* (3.7 g, 36 % yield) as colourless prisms, m.p. 167–169 °C. ^1H NMR (60 MHz, $CDCl_3$): δ 7.00 (3H, s), 2.13 (6H, s), 1.30 (9H, s).

This anilide (3.9 g, 0.019 mol) was added in portions to a solution of $LiAlH_4$ (0.9 g, 0.023 mol) in dry ether (50 ml). After 1 h at ambient temperature the mixture was refluxed for 26 h. After cooling, water (1 ml), 15 % NaOH (aq.) (1 ml) and water (3 ml) were added in this order. A white precipitate was removed by filtration (with suction), and the organic phase was dried with $MgSO_4$ and evaporated. Addition of hexane to the residue left unreacted starting material undis-

Table 1. Substituents in compounds *4–14* (see structure *3*), fractional population of the *E* form and $\Delta G^{\ddagger}$ for the $E \rightarrow Z$ exchange.

Compound	X	Y	Z	R	R^1	R^2	P_E[a]	$\Delta G^{\ddagger}_{E \rightarrow Z}$/kJ mol^{-1}
4	O	CH_3	CH_3	CH_3	H	$C(CH_3)_3$	1.00	–
5	S	CH_3	CH_3	CH_3	H	$C(CH_3)_3$	1.00	–
6	O	CH_3	CH_3	$C(CH_3)_3$	H	$C(CH_3)_3$	1.00	–
7	S	CH_3	CH_3	$C(CH_3)_3$	H	$C(CH_3)_3$	0.84	86.9
8	O	CH_3	Cl	$C(CH_3)_3$	H	$C(CH_3)_3$	1.00	–
9	O	CH_3	Cl	$C(CH_3)_3$	H	$CH(CH_3)_2$	1.00	–
10	S	CH_3	Cl	$C(CH_3)_3$	H	$CH(CH_3)_2$	0.69	89.4
11	O	CH_3	CH_3	H	CH_3	CH_3	0.92	102.5
12	S	CH_3	CH_3	H	CH_3	CH_3	0.44	103.8
13	O	CH_3	CH_3	CH_3	CH_3	CH_3	1.00	–
14	S	CH_3	CH_3	CH_3	CH_3	CH_3	1.00	–

[a] At +25 °C in *o*-dichlorobenzene.

solved, and evaporation of the hexane solution and distillation gave N-*neopentyl-2,6-dimethylaniline* as a liquid (2.0 g, 55 % yield), b.p. 87–90 °C/0.4 kPa. ^{1}H NMR (60 MHz, $CDCl_3$): δ 6.67–7.23 (3H, m), 2.93 (1H, broad), 2.67 (2H, s), 2.27 (6H, s), 1.03 (9H, s). Acetyl chloride (0.25 g, 0.003 mol) was added dropwise with stirring to a solution of the above aniline (0.6 g, 0.003 mol) in 1,2-dichloroethane (10 ml) with anhydrous sodium carbonate (0.4 g) at +10 °C. After reflux for 22 h the mixture was filtered hot and evaporated to give *4* (0.6 g, 86 % yield) as a colourless liquid, finally purified by PTLC. MS [IP 70 eV; *m/e* (% rel. int.)]: 233 (3, M), 218 (2, M–CH_3), 134 (100, M–CH_2CO–C_4H_9).

N-*Neopentyl-2,6-dimethylthioacetanilide* (*5*) was obtained from *4* in 59 % yield by method A as a pale yellow liquid, purified by PTLC. MS: 249 (6, M), 71 (100).

N-*Neopentyl-2,6-dimethylpivalanilide* (*6*) was prepared as *4* from *N*-neopentyl-2,6-dimethylaniline and pivaloyl chloride and was obtained in 57 % yield as colourless crystals, m.p. 67–68 °C. MS: 260 (1, M–CH_3), 57 (100, C_4H_9).

N-*Neopentyl-2,6-dimethylthiopivalanilide* (*7*) was obtained from *6* by method B in 40 % yield as pale yellow prisms, m.p. 81–82 °C. MS: 291 (4, M), 276 (3, M–CH_3), 71 (100).

N-*Neopentyl-2-chloro-6-methylpivalanilide* (*8*) was prepared analogously with *6*, starting from 2-chloro-6-methylaniline. The pivalanilide *8* was obtained in about the same yield as *6* as colourless prisms, m.p. 94–96 °C. MS: 280/282 (2.5/1.0, M–CH_3), 260 (3, M–Cl), 57 (100, C_4H_9).

N-*Isobutyl-2-chloro-6-methylpivalanilide* (*9*). N-*Isobutyl-2-chloro-6-methylaniline* was prepared in 71 % yield in the same way as *N*-neopentyl-2,6-dimethylaniline, starting from *2-chloro-6-methyl-butyranilide*. The pivalanilide *9* was obtained in 82 % yield analogously with *6* as colourless prisms, m.p. 53–54 °C. MS: 266/268 (2/1, M–CH_3), 246 (6, M–Cl), 57 (100, C_4H_9).

N-*Isobutyl-2-chloro-6-methylthiopivalanilide* (*10*) was obtained from *9* by method B in 39 % yield as pale yellow prisms, m.p. 54–56 °C. MS: 262 (5, M–Cl), 57 (100, C_4H_9).

N-*Isopropyl-2,6-dimethylformanilide* (*11*). The method described by Schellenberg[16] for the preparation of *N*-isopropylamines was adapted to N-*isopropyl-2,6-dimethylaniline*, which was obtained from 2,6-dimethylaniline as a colourless liquid in 61 % yield, b.p. 88–98 °C/3.7 kPa. ^{1}H NMR (60 MHz, $CDCl_3$): δ 6.5–7.2 (3H, m), 3.37 (1H, septet, *J* 7.0 Hz), 2.87 (1H, s), 2.23 (6H, s), 1.08 (6H, d, *J* 7.0 Hz).

Formylation with formic acetic anhydride according to Huffman[17] gave *11* as a colourless liquid in 98 % yield, finally purified by PGC.

Table 2. ^{1}H Chemical shifts[a] of alkyl groups in *4–14*.

Compound	ArCH_3	R	[R_1, R_2]	
4E	2.31	1.71 (CH_3)	3.45 (CH_2)	0.93 ($C(CH_3)_3$)
5E	2.26	2.23 (CH_3)	4.22 (CH_2)	0.97 ($C(CH_3)_3$)
6E	2.35	0.93 ($C(CH_3)_3$)	3.45 (CH_2)	0.93 ($C(CH_3)_3$)
7E	2.36	1.22 ($C(CH_3)_3$)	4.34 (CH_2)	0.98 ($C(CH_3)_3$)
7Z	2.18	1.61 ($C(CH_3)_3$)	4.04 (CH_2)	0.77 ($C(CH_3)_3$)
8E	2.34	1.02 ($C(CH_3)_3$)	3.29, 3.69 (CH_2)[b]	0.93 ($C(CH_3)_3$)
9E[c]	2.34	1.03 ($C(CH_3)_3$)	3.39, 3.43 (CH_2)[d]	1.96 (CH)[e] 0.93, 0.95 ($CH(CH_3)_2$)[f]
10E[c]	2.31	1.22 ($C(CH_3)_3$)	3.93, 4.23 (CH_2)[d,g]	1.87 (CH)[e] 0.93 ($CH(CH_3)_2$[f]
10Z[c]	2.71	1.57 ($C(CH_3)_3$)	3.86, 4.02 (CH_2)[d,h]	2.20 (CH)[e] 0.80, 0.91 ($CH(CH_3)_2$[f]
11E	2.18	7.74 (H)	4.19 (CH)	1.22 (CH_3)
11Z	2.24	8.28 (H)	3.71 (CH)	1.40 (CH_3)
12E	2.17	9.12(H)	5.07 (CH)	1.26 (CH_3)
12Z	2.16	9.53 (H)	3.84 (CH)	1.44 (CH_3)
13E	2.20	1.60 (CH_3)	4.39 (CH)	1.12 (CH_3)
14E	2.15	2.14 (CH_3)	5.37 (CH)	1.18 (CH_3)

[a] In ppm, downfield from TMS. Solvent $CHCl_2F$+$CHClF_2$ unless otherwise stated, ambient temperature. [b] AB system. [c] Solvent $CDCl_3$. [d] AB part of an $ABMX_6$ system. [e] M part of an $ABMX_6$ system. [f] X part of an $ABMX_6$ system. [g] J_{AB}=13.2 Hz. [h] J_{AB}=14.1 Hz.

MS: 191 (78, M), 176 (46, M−CH_3), 148 (100).

N-*Isopropyl-2,6-dimethylthioformanilide* (*12*) was obtained from *11* by method A in 40 % yield as pale yellow prisms, m.p. 77–79 °C. MS: 207 (48, M), 192 (13, M−CH_3), 132 (100).

N-*Isopropyl-2,6-dimethylacetanilide* (*13*) was prepared from *N*-isopropylaniline analogously to *4* in 81 % yield as a colourless liquid, finally purified by PTLC. MS: 205 (12, M), 190 (3, M−CH_3), 84 (100).

N-*Isopropyl-2,6-dimethylthioacetanilide* (*14*) was obtained in 82 % yield from *13* by method A. Pale yellow prisms, m.p. 54–56 °C. MS: 221 (18, M), 146 (100).

Variable-temperature ^1H NMR spectra were recorded on a JEOL model MH-100 NMR spectrometer equipped with a standard variable temperature attachment (VT 3-c). The samples for low temperature studies were *ca* 0.5 M in a mixture of dichlorofluoromethane and chlorodifluoromethane (FREON 21 and 22, *ca* 1:1), and they were degassed by repeated cycles of freeze-thawing before being sealed off under high vacuum. Tetramethylsilane was added with the solvent to provide the internal lock signal. High temperature spectra were recorded on solutions in *o*-dichlorobenzene with octamethylcyclotetrasiloxane for the lock. The temperatures were measured by monitoring the voltage of the internal thermocouple of the instrument and calibrating it at each experiment against an external thermocouple placed in a dummy tube containing the appropriate solvent.

The populations and rate constants were evaluated by visual fitting of the experimental spectra to spectra calculated by the McConnell formalism for uncoupled two-site exchange systems.[18,19] The calculations were performed on a PDP 11/34 computer with a GT 42 graphics terminal and a Printronix lineprinter/plotter of the Computer Graphics Laboratory for Organic Chemistry of the University of Lund.

The evaluation of T_2 values for bandshape calculations was based on the bandwidths of reference signals unperturbed by exchange as described previously.[20]

Table 3. Force field parameters.

Torsional constants Angle	V_1	V_2	V_3/kJ mol^{-1}
C−C−N(sp^2)−C(sp^2)	0.00	0.00	4.19
H−C−N(sp^2)−C(sp^2)	0.00	0.00	4.19
S=C−N(sp^2)−C(sp^2)	0.00	25.12	0.00
C−C_{CO}−N(sp^2)−C(sp^2)	0.00	25.12	0.00
C(sp^2)−C(sp^2)−N(sp^2)−C	0.00	0.00	0.00
C(sp^2)−C(sp^2)−N(sp^2)−C_{CO}	0.00	0.00	0.00
C−C(sp^2)−C(sp^2)−N(sp^2)	0.00	68.04	0.00
C(sp^2)−C(sp^2)−C(sp^2)−N(sp^2)	0.00	68.04	0.00
N(sp^2)−C−C−C	0.00	0.00	2.22
H−C−C=S	0.00	0.00	−5.23
S=C−N(sp^2)−C	0.00	25.12	0.00

Stretching constants Bond	L_o/Å	k_s/mdyn Å^{-1}
C(sp^2)−N(sp^2)	1.449	3.40
C=S	1.626	5.14

Bending parameters Angle	θ_o/deg.	k_b/mdyn Å rad^{-2}
C(sp^2)−C(sp^2)−N(sp^2)	120.0	0.60
C(sp^2)−N(sp^2)−C_{CO}	121.0	0.70
C−N(sp^2)−C(sp^2)	115.0	0.50
H−C=S	125.0	0.25
N(sp^2)−C=S	125.0	0.50
C−C=S	122.3	0.40
C=S	0.00	0.80

The free energies of activation were calculated using eqn. 1, which is based on the Eyring equation.[21]

$$\Delta G^{\ddagger}_{E\rightarrow Z}=1.914\cdot 10^{-2}T[10.319+\log(T/k_{E\rightarrow Z})] \quad (1)$$

The $E\rightarrow Z$ stereomutation of *12* was studied by monitoring the integrals of the thioformyl proton resonances as a function of time. The rate constant $k_{E\rightarrow Z}$ was evaluated from a least-squares semilogarithmic plot based on eqn. 2, using also eqn. 3,[22] where $I_{E,0}$ $I_{E,t}$, and $I_{E,e}$ represent the relative integrals of the *E* proton resonance at $t=0$, t, and ∞. At 47.0 °C, $k_{E\rightarrow Z}=(6.7\pm0.5)\cdot 10^{-5}$ s^{-1}.

$$(k_{E\rightarrow Z}+k_{Z\rightarrow E})t=\ln\frac{I_{E,0}-I_{E,e}}{I_{E,t}-I_{E,e}} \quad (2)$$

$$K=\frac{k_{Z\rightarrow E}}{k_{E\rightarrow Z}}=\frac{I_{E,0}-I_{E,e}}{I_{E,e}} \quad (3)$$

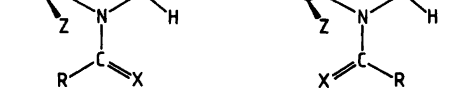
The molecular mechanics calculations were performed using the program developed by Allinger and co-workers with their 1973 force field (MMP1).[11,12] The parameters describing the (thio)amide skeleton were those used successfully for the calculation of ground state energies[1,6,23] and rotational barriers[24] in relatively strained amides and thioamides. The parameters not given previously are found in Table 3.

RESULTS AND DISCUSSION

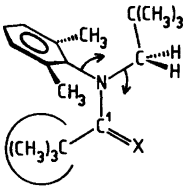
Shvo *et al.*[25] have studied a series of compounds (*15*), which show similarities with those in our work. In *15*, R=H, alkyl or aryl, and in all compounds except the formamide, only one rotamer is observed. This is shown by the aromatic solvent induced shift (ASIS)[26,27] method to be the *E* form, and also in the formamide this form dominates strongly. Similar compounds have been studied by Siddall and Stewart[28] with equivalent results. *N*-Methylacetanilide has been shown by NMR spectroscopy[29] and X-ray crystallography[30] to be predominantly (99.5 % in solution, exclusively in the crystal) in the *E* form with the benzene ring orthogonal to the amide plane.

Several authors[29,31,32] have reported considerable shift differences for the acyl group protons in the *E* and *Z* forms of anilides, with the *E* form resonances in general at higher field. Rae[33] has shown that increased deviation from coplanarity of the aromatic ring increases the shift difference in a series of ortho-substituted formanilides because of increased shielding in the *E* form, a result which is supported by model calculations using the shielding data of Johnson and Bovey.[34] However, in some formanilides the formyl proton in the *E* form is *less* shielded than that in the *Z* form.[32,35]

The assignment of *E* and *Z* rotamers in the compounds *4–14* is mostly straightforward. It can be based on the shifts of the R protons, and as references we have used the shifts in the analogous *N,N*-diisopropyl-[6] and *N,N*-dineopentyl- and -isobutyl(thio)amides,[1] when available. In the afore-mentioned compounds, the acetylmethyl proton resonances fall in the narrow range of δ 2.01–2.15 with the higher values for the more crowded environments. The corresponding range for thioacetamides is δ 2.63–2.79. The acetyl ^{1}H resonances in *4* and *13* fall at δ 1.71 and 1.60. Thus these rotamers are assigned to the respective *E* forms. Similarly, the thioacetyl ^{1}H resonances in *5* and *14* fall at δ 2.23 and 2.14, and must also be ascribed to the *E* form. The ^{1}H resonances of the (thio)pivaloyl groups in *N,N*-diisopropyl pivalamide and -thiopivalamide fall at δ 1.26 and *ca* 1.40 respectively,[24] and the compounds with more shielded t-Bu protons (*6*, *8*, major rotamer of *7* and minor rotamer of *10*)



3 E *3 Z*



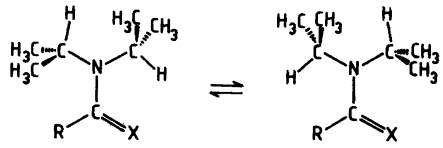
6 E, X = O
7 E, X = S

are assigned to the *E* form. To support these conclusions, the ring current shieldings of acetyl and pivaloyl protons in *E* forms of the (thio)acet-

and (thio)pivalamides were calculated, using the tables of Haigh and Mallion.[36] The geometric data required were taken, for the (thio)acetanilides from the MMP1 energy-minimized structure of *5E* (*vide infra*), and for the (thio)pivalanilides from a standard geometry (standard bond lengths from MMP1, all angles at sp^2 atoms 120° and at sp^3 atoms 109.5°). For the (thio)acetyl protons an average shielding of 0.14 ppm and for the (thio)pivaloyl protons one of 0.17 ppm was calculted, in general somewhat less than but of the same order of magnitude as the observed differences between the *N,N*-dialkyl(thio)amides and the corresponding *E*-(thio)anilides.

All compounds, which show two rotamers with respect to the CX–N bond (*7, 10, 11,* and *12*) were studied both in FREON and in *o*-dichlorobenzene as solvent. Without exception, the resonances of the ring methyl and *N*-alkyl protons being *anti* to the (thio)carbonyl group with respect to the CX–N bond showed larger upfield shifts in the aromatic solvent than those being *syn*, thus supporting the assignments made in Tables 1 and 2.

N,N-Diisopropylamides and -thioamides normally exist as mixtures of two major rotameric forms *16A* and *16B*. The equilibrium between



16 A *16 B*

them is shifted toward the *B* form by increasing size of R or decreasing size of X, and from the position of the equilibrium a scale of relative sizes of a series of R and X can be established. The scale emerging from compounds *16* can be given as:[6,7,37]

$$H \approx O < iPr < CH_3 \approx S < tBu$$

The scale can be used to assess the steric requirements of different groups R^1 and R^2 in other *N,N*-disubstituted {thio}amides *17*. Here, the larger of R and X will prefer to be on the same side of the C^1–N bond as the smaller of R^1 and R^2. In this way we can establish that R^1=aryl is smaller than methyl and other alkyl groups,

17 A *17 B*

since already in *N*-methylacetanilide the *E* form is 99.5 % of the equilibrium mixture.[29] This is also in agreement with the dominance of the *E* form in all anilides in this work, and also in that reported in Refs. 25 and 28.

However, with the thioanilides, the situation is not quite so straightforward. In the thioformanilide *12* the *Z* form dominates, but in the thioacetanilides *5* and *14* only the *E* forms can be observed, as is also the case with *N*-benzyl-*o*-methyl-thioacetanilide.[28] When the size of the R group is increased, as in *7* and *10*, the *Z* form appears again. In the standard geometry used to calculate the shielding in the *E* form of *7*, the shortest distance between a hydrogen atom in the pivaloyl group and a carbon atom in the benzene ring is 220 pm, compared to 335 pm for the sum of the van der Waal's radii. Clearly a considerable repulsion must occur also in the *E* form, and the balance of the repulsions on both sides of the C^1–N bond leads to a relative favorization of the *Z* form. This is not observed in the analogous pivalanilide *6*, possibly because the smaller oxygen atom permits a larger deflection of the *N*-neopentyl group and the benzene ring away from the pivaloyl tBu group than can occur in *7*. Similar considerations apply to *9* and *10*.

The free energy barriers to rotation of the thiopivaloyl group in *7* (87 kJ mol^{-1}) and *10* (89.5 kJ mol^{-1}) reveal some ground-state strain, whereas the high barriers in *11* and *12* indicate essentially unstrained ground states but possibly strained transition states. The barrier in *12* is high enough to allow the separation of the *E* form in pure state by chromatography on silica. The rate of *E*→*Z* transformation could then be followed by direct stereomutation at 47 °C. The barrier thus measured shows no difference from the one measured by bandshape analysis at 176 °C, indicating an activation energy close to zero.

The isolation of pure *E*–*Z* rotamers from 2,6-disubstituted anilides and thioanilides has been reported previously.[31,38]

We now come to the question of the conformations of the *N*-alkyl groups, and we begin with the

N-neopentyl compounds *4* to *8*. If the neopentyl group assumes a perpendicular or nearly perpendicular orientation with respect to the (thio)amide plane, the methylene protons are diastereotopic, and their ^{1}H NMR spectrum should appear as an AB system on slow rotation.[1] This is not observed in the available temperature region (≥ -130 °C) except for compound *8*, where the anisochrony is ascribed to the chiraly caused by slow rotation of the 2-methyl-6-chlorobenzene ring (*vide infra*). In compounds *4* to *7* the methylene protons have the (thio)amide plane as a time-average plane of symmetry, and this may arise because of fast exchange between two enantiomeric, more or less perpendicular orientations or because the molecule exists in one single energy minimum with a plane of symmetry. Since the NMR spectra give little information on this, we have performed MMP1 calculations on *5E* with special consideration of the effect of rotation around the N–CH_2 bond. The lowest energy minimum (total strain energy 66.3 kJ mol^{-1}) is found for a conformation with the benzene ring perpendicular to the thioamide plane and with the neopentyl group symmetrically bisected by this plane and *anti* to the thiocarbonyl group (Fig. 1). Rotation by *ca.* 40° in either direction leads to maxima 12.9 kJ mol^{-1} above the lowest minimum, and then at *ca.* ±90° rotation two enantiomeric minima are found only 0.9 kJ mol^{-1} above the lowest minimum. On continued rotation, the energy increases to a maximum of *ca.* 30 kJ mol^{-1} above the lowest minimum, when the *t*-butyl group eclipses the thiocarbonyl group.

Similar calculations on *5Z* gave a pair of minima at *ca.* ±90° rotation with a total strain energy of 78.5 kJ mol^{-1} (12 kJ mol^{-1} above the *E* form), supporting the assignment of the *E* conformation to the only observed rotamer.

The ring-current shielding of the *t*-Bu group in *5E* is calculated to be 0.14 and 0.03 ppm, respectively, for the minima, and the population-weighted mean is 0.08 ppm. In agreement with this, the *t*-Bu proton resonance appears at δ 0.97 compared to δ 1.08 for the similarly situated neopentyl group in *N,N*-dineopentylthioacetamide.[1]

The very strong shielding of the neopentyl *t*-Bu protons in *7Z* (δ 0.77) is best exlained by a deformation due to the proximity of the thiopivaloyl *t*-Bu group, which pushes the *N*-neopentyl group into a more strongly shielding region closer to the aromatic ring.

The situation with respect to rotation of the isopropyl groups in compounds *11* to *14* is similar. No splitting of the isopropyl resonances due to slow rotation about the N–iPr bond can be observed above −130 °C. MMP1 calculation of the energy of *12E* as a function of the H–$C(CH_3)_2$–N–CHS dihedral angle gave a very flat energy curve with the two deepest minima at angles of ±45° from the state where the iPr methine proton eclipses the thiocarbonyl group (Fig. 2), and a second pair of minima, 4.9 kJ mol^{-1} higher, at ±160°. The pair of highest energy maxima, 16.4 kJ mol^{-1}, is found at ±110°, *i.e.* in states where one of the iPr methyl groups nearly eclipses the thiocarbonyl group. In the ±45° conformation, the methine proton is still in the strongly deshielding region of the thiocar-

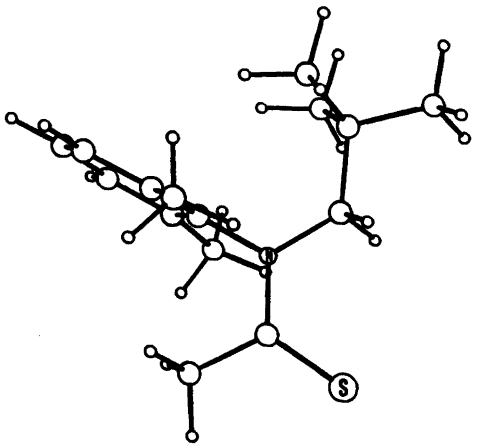


Fig. 1. Minimum energy conformation of *5E*.

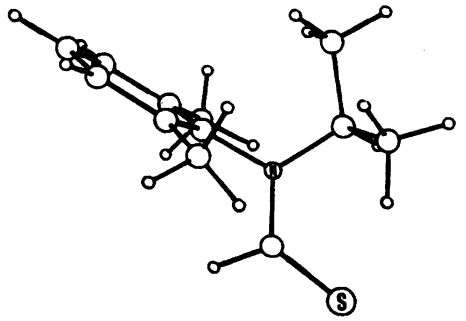
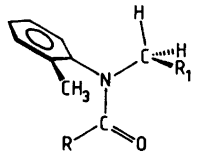


Fig. 2. Minimum energy conformation of *12E*.

bonyl group,[39] which fits with its resonance at δ 5.07, compared to 3.84 in *12Z* and 5.67 for the methine proton eclipsing the thiocarbonyl group in *N,N*-diisopropylthioformamide (*16B*, R=H, X=S).[6]

Calculations for *12Z* gave two pairs of energy minima, with the H−CMe_2−N−CSH dihedral angle at ±47 and at ±168°. The former minima are the lowest by 1.9 kJ mol^{-1}, and they are also 3.7 kJ mol^{-1} lower than the lowest minima in *12E*. Thus the calculations support the assignment of the low energy rotamer of *12* to the *Z* form. It also appears from the calculations that the face of the aromatic ring presents little hindrance to the rotation of the isopropyl group in *12* (and presumably even less in *11*).

The third type of process, the rotation of the aromatic ring, can for symmetry reasons only be observed in the 2-methyl-6-chloroanilides *8, 9,* and *10*. In *8* the neopentyl methylene proton resonance appears as an AB quartet, and in *9* and *10* the isobutyl methyl proton resonances appear as doublets of doublets, and the methylene proton resonances as the AB parts of a ABM system. None of these groups of signals shows any discernable band broadening due to exchange below +170 °C, which means that the rate constants for rotation of the aryl groups are less than 1 s^{-1} at this temperature. This gives a lower limit to the free energy to the rotation of 110 kJ mol^{-1}, corresponding to a half-life at +25 °C in excess of 24 d. Consequently, these compounds should be resolvable in optical antipodes, which has also been demonstrated by chromatography on microcrystalline triacetylcellulose. We will report on the resolution, the CD spectra, and the rates of racemization of these compounds in a forthcoming publication.



15 E

The barrier to rotation of the *o*-totyl ring in *N*-benzyl-2-methylacetanilide (*15E*, R=CH_3) is 84 kJ mol^{-1},[25] and in the analogous formamide the corresponding barriers are 54 kJ mol^{-1} and 42 kJ mol^{-1} in the *Z* and *E* forms, respectively.[28] In 2,6-diisopropylacetanilide (*18*), the barriers to rotation of the aromatic ring are 79 and 49 kJ mol^{-1} in the *E* and *Z* forms, respectively.[40] Similar barriers are found in other secondary 2,6-diisopropyl(thio)anilides, whereas the tertiary analogues have $\Delta G^{\ddagger} > 100$ kJ mol^{-1}.[41] Evidently the high barriers in the latter compounds as well as in *8, 9,* and *10* are due to the necessity for the simultaneous passage of one ortho substituent past the (thio)acetyl group and the other past the *N*-substituent.

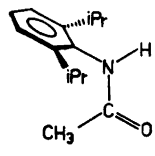
CONCLUSION

The result of this study is that primary alkyl groups attached to an sp^2 hybridized nitrogen atom with a (thio)acyl group and a 2,6-disubstituted aromatic ring as flanking groups may take up the customary perpendicular orientation (*2*), but that a conformation with R pointing towards the face of the aromatic ring is about equally probable even in the case when R=*t*-Bu. The barrier between these two conformations is quite low.

For isopropyl groups, the stable conformation is not the symmetrical bisected one (*1*), but one with less symmetry, in which the methyl groups point in the direction of the aromatic ring.

For both types of substituents, the face of the aromatic ring presents a small hindrance to the motion of adjacent alkyl groups.

This is in agreement with previous observations of the conformational dependence of the size of an aromatic ring. Thus, the ΔG°_{x} value for a phenyl group in cyclohexane is larger than that of a methyl group (12.5 *versus* 7.1 kJ mol^{-1}).[42] The high energy of the axial phenyl group is probably due to "edge-on" interactions between the ortho protons and the equatorial protons in positions 2 and 6 in a conformation, in which the phenyl group is perpendicular to the 1-CH bond. In a parallel conformation, strong interactions



18E

between the ortho protons and the axial 3-H and 5-H atoms would have given an even higher energy.[9] In 2,2-dimethyl-3-substituted butanes on the other hand, the steric effect of a 3-phenyl ring on the rotation of the *t*-butyl group is *smaller* than that of a 3-methyl group, at least partly because the *t*-butyl group rotates against the face of the phenyl ring.[43]

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