Conformational Equilibria and Torsional Barriers of the Isopropyl Groups in *N,N*-Diisopropylbenzamide and its Thio and Seleno Analogues

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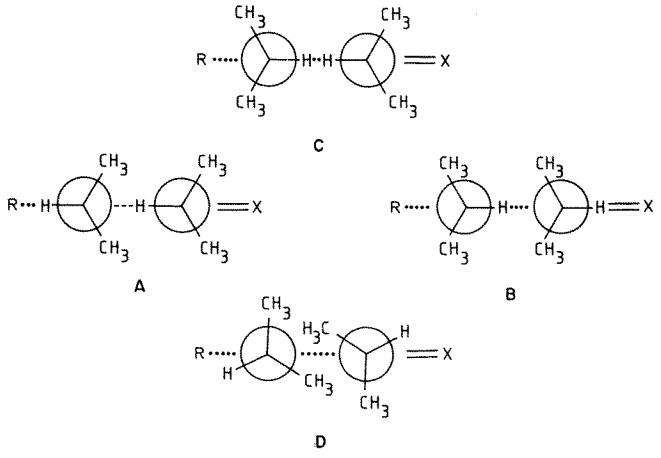
The conformations of the isopropyl groups and the barriers to conformational interconversion in *N,N*-diisopropylbenzamide (1), and its thio (2) and seleno (3) analogues have been studied by dynamic ^{1}H NMR spectroscopy. In 1 only one conformation is observed, whereas 2 and 3 exist as mixtures of three conformations. The use of the strongly deshielding C=X (X = O, S, Se) group and comparison with earlier results on similar systems allows total assignment, in the case of 2, rectifying an earlier proposal. The temperature dependence of the NMR spectra of 2 and 3 clearly shows that the *E*- and *Z*-isopropyl groups rotate with very different rates, thus providing experimental evidence for the stepwise nature of the conformational interchange.

INTRODUCTION

The conformations and barriers to conformational interchange of the isopropyl groups in *N,N*-diisopropylamides, -thioamides and -selenoamides have been extensively studied.[1–8] Four general types of conformations, A–D (Scheme 1), exist, and their relative energies depend on the effective sizes of the flanking groups, R and X.

Usually conformations of types A and B predominate, and form B is favoured by a large X combined with a small R, whereas a small X and a large R favour form A. Conformations of type D should be regarded as an equilibrium between two rapidly exchanging enantiomers, and are favoured by two large flanking substituents, R and X. Many *N,N*-diisopropyl-thioamides and -selenoamides have been shown to exist as a mixture of A, B and, in some cases, D.[1–3] The conformations of the isopropyl groups in *N,N*-diisopropylthiobenzamide have been studied by ^{1}H NMR at low temperature by Ramey *et al.*[7] They reported two conformations, the major of which was suggested to be of type D and the minor of type B. This is at variance with the general behaviour of other *N,N*-diisopropyl(thio)amides.[1–3] We decided to make a reinvestigation of the conformations of the isopropyl groups in *N,N*-diisopropylthiobenzamide (**2**) and to include the oxygen (**1**) and seleno analogues (**3**) in this study.



Scheme 1

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EXPERIMENTAL

Syntheses

***N,N*-Diisopropylbenzamide (1).** Prepared from diisopropylamine and benzoyl chloride in toluene in quantitative yield, giving white prisms, m.p. 72–74 °C (lit.[9] 69–71 °C). ^{1}H NMR ([$^2H_6$]dimethyl ether, 25 °C), δ 1.30 (12H, broad), 3.67 (2H, broad), 7.23–7.35 (5H, m).

***N,N*-Diisopropylthiobenzamide (2).** Prepared according to Ref. 10 from **1** in quantitative yield, giving yellow prisms, m.p. 100–102 °C (lit.[7] 99–100 °C). ^{1}H NMR ([$^2H_6$]dimethyl ether, 25 °C), δ 1.15 (6H, d, J = 7.00 Hz), 1.75 (6H, broad), 4.10 (2H, sept., J = 7.00 Hz), 7.05–7.28 (5H, m); *m/e* 221 (12%), 178 (25), 162 (5), 121 (100), 105 (52), 77 (31), 51 (10), 41 (24).

***N,N*-Diisopropyl[α-(methylthio)benzylidene]ammonium iodide (4).** This compound $C_6H_5(CH_3S)C{=}\overset{+}{N}[CH(CH_3)_2]_2I^-$ was prepared from **2** and methyl

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iodide in 74% yield as colourless crystals, m.p. 141–143 °C.

N,N-Diisopropylselenobenzamide (3). Prepared from **4** and ethanolic sodium hydrogen selenide[11] in 26% yield, giving yellow prisms, m.p. 113–114 °C (lit.[12] 112.0–113.5 °C). ^{1}H NMR ([$^2H_6$]dimethyl ether, 25 °C), δ 1.16 (6H, d, J = 6.80 Hz), 1.85 (6H, broad), 4.18 (2H, sept., J = 6.80 Hz), 7.04–7.28 (5H, m); *m/e* 269 (11%), 226 (13), 169 (38), 146 (7), 123 (31), 104 (100), 91 (12), 77 (50), 58 (78), 51 (19), 41 (94).

^{1}H NMR spectra. The spectra were recorded on a Nicolet 360 WB spectrometer. The samples were approximately 0.04 M in [$^2H_6$]dimethyl ether,[1] and were degassed by the high-vacuum freeze–thaw technique before being sealed off. Me_4Si was used as internal reference. Band shape analysis was performed as described previously.[13] The free energy differences and the free energies of activation were calculated using Eqns (1) and (2), where p_A is the fractional molar population of conformation A.

$$\Delta G^0 = 8.314 \times 10^{-3} T \ln (p_A/p_B) \text{ kJ mol}^{-1} \quad (1)$$

$$\Delta G^{\ddagger} = 1.914 \times 10^{-2} T[10.319 + \log (T/k)] \text{ kJ mol}^{-1} \quad (2)$$

The band shape calculations were performed on a PDP 11/34 computer with a GT 42 graphics terminal and a Printronix line printer/plotter of the Computer Graphics Laboratory for Organic Chemistry at the University of Lund.

RESULTS

The ^{1}H NMR spectra at ambient temperature indicate that the rotation around the N—C(=X) bond is slow for **2** and **3**, but has still some influence on the band shape for **1**. The barriers to rotation around this bond in *N,N*-dimethylbenzamide and its thio, seleno and telluro analogues have been studied elsewhere[14] and will not be treated here.

The chemical shifts of the isopropyl groups and fractional populations at low temperature are shown in Table 1 and the free energy barriers to isopropyl group rotation in Table 2.

N,N-Diisopropylbenzamide (1)

At ambient temperature, the NMR signals for **1** are broad owing to fast amide bond rotation. On lowering the temperature the signals sharpen (−45 °C) and remain sharp at still lower temperature (−90 °C), and only two doublets and two septets were observed for the isopropyl ^{1}H NMR resonances.

Table 2. Free energy barriers to isopropyl group rotation in compounds 2 and 3

Compound	Temperature (K)	$\Delta G^{\ddagger}_{A\rightarrow(B+D)}$ (kJ/mol)	Temperature (K)	$\Delta G^{\ddagger}_{D\rightarrow B}$ (kJ/mol)
2	269	55.3±0.8 (13.2±0.2)[a]	198	38.9±0.8 (9.3±0.2)[a]
3	291	57.4±0.8 (13.7±0.2)[a]	216	37.3±0.8 (8.9±0.2)[a]

[a] Values in parentheses in kcal mol^{-1}.

N,N-Diisopropylthiobenzamide (2)

The NMR spectrum for **2** shows two signals for the (*E*)- and (*Z*)-isopropylmethyl groups, at ambient temperature, due to slow amide bond rotation. The NMR signal for the (*Z*)-isopropylmethyl groups is broad and, on lowering the temperature, the signal splits into two doublets of relative intensities 0.95:0.05 (−46 °C). The (*Z*)-methine resonance behaves similarly, giving rise to a major septet at δ 4.0 and a minor septet at δ 6.1 below −46 °C. At still lower temperature a broadening of the minor component sets in and the signals split, at −102 °C, into two sets of signals with relative intensities 0.35:0.65. The barrier for the process which leads to decoalescence above −46 °C ± is 55.3 0.8 kJ mol^{-1} (13.2± 0.2 kcal mol^{-1}) (269 K) and for the second process 38.9 ±0.8 kJ mol^{-1} (9.3 ±0.2 kcal mol^{-1}) (198 K).

N,N-Diisopropylselenobenzamide (3)

In conformity with **2**, the NMR spectrum for **3** shows two doublets for the (*E*)- and (*Z*)-isopropylmethyl groups, at ambient temperature, and the signal for the (*Z*)-isopropylmethyl groups is broad and undergoes decoalescence at −33 °C to two sets of signals with relative intensities 0.81:0.19. At still lower temperature the signals for the minor component broaden (−70 °C) and split into two sets of signals (−105 °C) with relative intensities 0.26:0.74 (Fig. 1). The barrier for the process which leads to decoalescence above −33 °C is 57.4±0.8 kJ mol^{-1} (13.7±0.2 kcal mol^{-1}) (291 K) and for the second process 37.3 ±0.8 kJ mol^{-1} (8.9±0.2 kcal mol^{-1}) (216 K).

Table 1. Chemical shifts[a] and fractional populations of compounds 1–3

Compound	Temperature (°C)	Rotamer A CH_3-(Z)	CH-(Z)	CH_3-(E)	CH-(E)	p[b]	Rotamer B CH_3-(Z)	CH-(Z)	CH_3-(E)	CH-(E)	p[b]	Rotamer D CH_3-(Z)	CH-(Z)	CH_3-(E)	CH-(E)	p[b]
1	−90	1.52	3.81	1.12	3.53	1.0										
2	−110	1.81	4.03	1.13	4.03	0.95	1.28	6.03	1.04	4.03	0.035	1.48	5.95	1.13	4.03	0.015
3	−105	1.92	4.20	1.15	4.10	0.87	1.33	6.25	1.06	4.20	0.104	1.55	6.10	1.33	4.40	0.026

[a] In ppm downfield from internal Me_4Si, in dimethyl-d_6 ether.
[b] Fractional population.

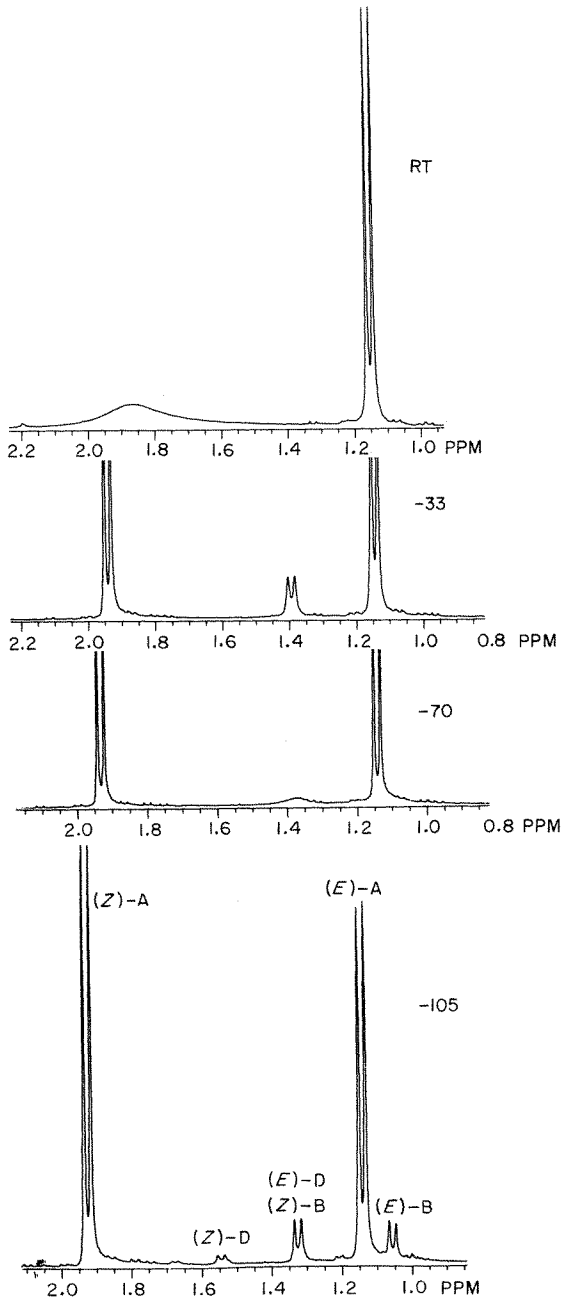

Figure 1. 360 MHz ^{1}H NMR spectrum of **3** in [$^2H_6$]dimethyl ether at different temperatures showing the isopropyl doublet region.

DISCUSSION

The chemical shift for a (*Z*)-isopropylmethyl group in *N,N*-diisopropylamides is found at *ca* δ 1.40 when it points towards the carbonyl group, and at *ca* δ 1.10 when it is turned away from the carbonyl group.[1–3] The chemical shift for a (*Z*)-methine hydrogen is found at δ 4.5–5.2 when it points towards the carbonyl group and at δ 3.3–3.6 otherwise.[1–3] In view of these results, we ascribe the only observed rotamer for **1** to a conformation of type A. This is in agreement with other amides where the carbonyl group has also been shown to have small steric requirements.[1–3]

The chemical shift for a (*Z*)-isopropylmethyl group in *N,N*-diisopropylthioamides is found at δ 1.7–1.8 and for a (*Z*)-methine hydrogen at δ 5.5–6.3 when they point towards the thiocarbonyl group.[1–3] The corresponding values are δ 1.2–1.4 and δ 3.8–4.1 when the isopropyl group is turned away from the thiocarbonyl group.[1–3] In view of the results obtained on several similar systems, we consider the previous assignment by Ramey *et al.*[7] for **2** as incorrect. A more likely assignment for the major rotamer is a conformation of type A, and the two minor components we ascribe to conformations of type B and D.

In order to assign these rotamers we make use of the positions of the (*Z*)-isopropylmethyl signals (δ 1.48 and 1.28) and the methine septets (δ 5.95 and 6.03). The attribution of B and D rests on the assumption that the predominant difference in chemical shift between B and D should come from the van der Waals shift induced in the (*Z*)-isopropylmethyl group resonance in conformation D and the position of the (*E*)-isopropylmethyl doublet at high field (δ 1.04 and 1.06) in conformation B, as expected for protons situated in the shielding region of the benzene ring. The same arguments are valid for the seleno compound. A typical shift for a (*Z*)-isopropylmethyl group in *N,N*-diisopropyl substituted selenoamides is *ca* δ 1.85 when pointing towards the selenocarbonyl group and δ 1.3–1.5 when turned away from it.[2] A (*Z*)-isopropylmethine hydrogen is found between δ 6.3 and 6.5 when it is turned towards the selenocarbonyl group and at *ca* δ 4.15 when it is turned away from the selenocarbonyl group.[2]

In all the compounds **1–3** conformation A is strongly preferred, and one can conclude that the bulky face of the isopropyl group, the methyl groups, accommodate much better with the C=X groups than with the phenyl group. This can be compared with the structurally related α-alkyl-β,β-diisopropylstyrenes,[15] in which the isopropyl groups interact with the phenyl group and the α-alkyl substituent. If the α-substituent is a methyl, ethyl or isopropyl group there is more than 98% of the conformation where the isopropyl groups turn the methyl groups towards the α-substituent. A much bulkier group, such as the *tert*-butyl group, is required in order to reverse the conformational preference.

The difference in populations between A and B+D diminishes in the series X = O, S and Se, i.e. with increasing size of X. The size of X is important in two respects: on the one hand in the interaction with the (*Z*)-isopropyl group and on the other in the interaction with the phenyl group which affects the dihedral angle between the N—C(X) moiety and the phenyl ring. Both of these effects tend to displace the equilibrium towards conformation B, when the size of X is increased. The dihedral angle between the amide plane and the phenyl ring in *N,N*-dimethylthiobenzamide is 63° in the crystal.[16] This angle could be expected to be larger in *N,N*-diisopropyl derivatives than in the corresponding *N,N*-dimethyl compounds and of the same magnitude as the angle between the phenyl ring and the double bond in α-alkyl-β,β-diisopropylstyrenes.[15] The twist angle in these compounds (α-alkyl = Me, Et, *i*-Pr, *neo*-Pent, and *t*-Bu) is *ca*

70–90° according to molecular mechanics calculations. A large twist between the amide plane and the phenyl ring is also revealed from the chemical shift of the (*E*)-isopropylmethyl groups in conformation B of **2** and **3** (δ 1.04 and 1.06, respectively).

The difference in population between conformations of type B and D for **2** and **3**, 0.65:0.35 and 0.74:0.26, respectively, can also be understood when regarding the dihedral angle around the pivot bond, which is assumed to be larger in the selenoamide, **3**, as discussed above.[14] This reduces the steric interaction between the (*E*)-isopropylmethyl groups and the phenyl ring in **3** compared with **2**, and favours conformation B in the seleno compound relative to the thio compound.

The effective size of the groups in these and analogous systems[1–3,15] can be estimated from the position of the conformational equilibria:

$$H \approx C{=}O < i\text{-}Pr < Me \approx Et \approx n\text{-}Pr < C{=}S < C{=}Se < Ph < CF_3 \approx t\text{-}Bu.$$

The assignments made above lead to the conclusion that the decoalescence observed at −46 °C for **2** and at −33 °C for **3** corresponds to the rotation of the (*Z*)-isopropyl group. The barrier for this rotation is slightly higher in **3** than in **2** (Table 2), possibly depending on the larger size of Se than S. The process affecting the spectrum at lower temperature is, consequently, the rotation of the (*E*)-isopropyl group and, in contrast to the aforementioned process, the barrier is slightly lower for **3** than for **2**. Of more significance, however, is the difference in torsional barrier between the (*E*)- and (*Z*)-isopropyl groups in both **2** and **3**. The rate constant for the rotation of the (*E*)-isopropyl group is roughly five orders of magnitude larger than the rate constant for rotations of the (*Z*)-isopropyl group ($\Delta S^{\ddagger}$ assumed zero in both cases), thus providing clear evidence for the stepwise nature of the conformational interchange, A ⇌ B. A comparison with earlier work[1,2] shows that the barrier to isopropyl rotation in *N,N*-diisopropyl-thio-, and -selenoamides falls in the range 50–60 kJ mol^{-1} and, therefore, the (*E*)-isopropyl barriers of **2** and **3** are low, whereas the (*Z*)-isopropyl barriers stay in the normal region. The low (*E*)-isopropyl barrier depends largely on a comparatively low transition-state energy, probably invoked by a higher degree of planarity of the PhC(X) system with concomitant more effective conjugation, and only to a minor part on high ground-state energies of the rotamers B and D.

CONCLUSIONS

The conformations of the isopropyl groups in *N,N*-diisopropylbenzamide (**1**) and the corresponding thio (**2**) and seleno (**3**) analogues have been studied by dynamic ^{1}H NMR spectroscopy. Compound **1** was shown to exist in only one conformation at low temperature. This conformation was ascribed type A (Scheme 1). **2** and **3** were shown to exist in three conformations, A, B and D, with relative intensities 0.95:0.035:0.015 and 0.87:0.104:0.026, respectively. The barrier for the (*Z*)-isopropyl group rotation for **2** was 55.3 ± 0.8 kJ mol^{-1} (13.2 ± 0.2 kcal mol^{-1}) and for **3** 57.4 ± 0.8 kJ mol^{-1} (13.7 ± 0.2 kcal mol^{-1}). The barrier for the (*E*)-isopropyl group rotation was 38.9 ± 0.8 and 37.3 ± 0.8 kJ mol^{-1} for compounds **2** and **3**, respectively. The mechanism for the exchange A ⇌ B was shown to be a stepwise rotation of the isopropyl groups.

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