Investigation of the Amide Rotation in *N,N*-Dialkylbenzamides

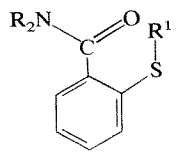
7*—Re-examination of the Role of the Hydrogen Bond in 2-Mercapto Substituted Derivatives†

Adam Gryff-Keller‡ and Przemysław Szczeciński
Department of Chemistry, Technical University of Warsaw, 00-664 Warsaw, Poland

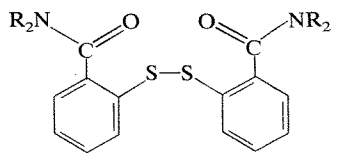
Barriers to the amide rotation in 2-mercapto-*N,N*-dialkylbenzamides [alkyl = CH_3 or $CH(CH_3)_2$] and some of their derivatives were measured by dynamic ^1H NMR. For *N,N*-diisopropylamides, barriers to rotation about the carbonyl—aryl bond were also determined. The results show that the intramolecular hydrogen bond has only a very small influence on the measured barriers. In contrast to the literature data, only one set of signals, common to all possible forms of 2-mercapto-*N,N*-dimethylbenzamide, has been observed.

INTRODUCTION

The existence of an intramolecular hydrogen bond in 2-mercapto-*N,N*-dimethylbenzamide (**1**) was first reported by Mires *et al.*[1] On the basis of NMR and IR measurements, they concluded that **1** assumed a coplanar conformation similar to that postulated for 2-hydroxy-*N,N*-dimethylbenzamide.[2] They observed only one *N*-CH_3 signal in the NMR spectrum of **1** in $CDCl_3$ at room temperature.[1] In contrast, in the spectrum reported by Fong[3] three pairs of *N*-CH_3 signals are present at 0 °C, which have been assigned to three different conformers of **1**. In this work, a non-coplanar structure of the investigated molecule was assumed. This assumption seems to be correct in view of the work of Jennings *et al.*,[4] in which non-coplanarity of some *o*-hydroxy-*N,N*-dialkylbenzamides was proved. Nevertheless, we decided to reinvestigate the problem because the NMR spectra of **1** reported by Fong[3] were in striking disagreement with the earlier data,[1] and many of the conclusions drawn by Fong seemed to be questionable. This paper reports the results of NMR investigations of **1** and its following derivatives: *N,N*-diisopropyl-2-mercaptobenzamide (**2**), *N,N*-dimethyl-2-methylthiobenzamide (**3**), bis[2-(*N,N*-dimethylcarbamoyl)phenyl] disulphide (**4**) and bis[2-(*N,N*-diisopropylcarbamoyl)phenyl] disulphide (**5**).



1 R = CH_3, R^1 = H;
2 R = $CH(CH_3)_2$, R^1 = H:
3 R = CH_3, R^1 = CH_3



4 R = CH_3;
5 R = $CH(CH_3)_2$

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‡ Author to whom correspondence should be addressed.

EXPERIMENTAL

Bis[2-(*N,N*)dimethylcarbamoyl)phenyl] disulphide (**4**) was prepared from 2,2′-dithiodibenzoic acid[5] according to the method described by Schindlbauer,[6] m.p. 129–132 °C (from CCl_4). Chemical shifts of *N*-Me signals at 20 °C: δ_Z = 3.126 ppm, δ_E = 2.837 ppm.

2-Mercapto-*N,N*-dimethylbenzamide (**1**) was obtained by reduction of **4** with zinc in acetic acid, by analogy with the reduction of 2,2′-dithiodibenzoic acid,[5] oil, b.p. 110 °C (0.4 mmHg). Chemical shifts of *N*-CH_3 signals at 20 °C: δ_Z = 3.140 ppm, δ_E = 2.881 ppm.

N,N-Dimethyl-2-methylthiobenzamide (**3**) was prepared by treating the potassium salt of **1** in absolute ethanol with an excess of methyl iodide; m.p. 48–51 °C, b.p. 110 °C (0.6 mmHg) [lit.,[7] b.p. 168–170 °C (10 mmHg)]. Chemical shifts of *N*-CH_3 signals at room temperature: δ_Z = 3.129 ppm, δ_E = 2.843 ppm. Chemical shift of SCH_3 signal: δ = 2.465 ppm.

Bis[2-(*N,N*-diisopropylcarbamoyl)phenyl] disulphide (**5**) was prepared by treating 2,2′-dithiodibenzoic acid dichloride, obtained from the acid and thionyl chloride, with an excess of diisopropylamine in benzene; m.p. 160–163 °C. Chemical shifts of isopropylmethyl signals at −46 °C (values in parentheses refer to the same isopropyl group): (1.096, 1.182 ppm), (*ca* 1.55, *ca* 1.55 ppm).

N,N-Diisopropyl-2-mercaptobenzamide (**2**) was prepared by reduction of **5** with Zn in acetic acid;[5] m.p. 99–102 °C. Chemical shifts of isopropylmethyl signals at −40 °C (values in parentheses refer to the same isopropyl group): (1.074, 1.188 ppm), (1.537, 1.561 ppm).

Elemental analysis data for compounds **2**, **4** and **5** were in agreement with the assigned structures.

$CDCl_3$ and CH_2Cl_2 were washed with aqueous sodium hydrogen carbonate solution, dried, distilled and kept over anhydrous K_2CO_3. Pyridine was dried with calcium hydride and distilled just before use.

NMR measurements were made on 0.2 M solutions

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of **1–5** in $CDCl_3$ or pyridine or, in the case of the low-temperature spectra of **5** on a 0.02 M solution in CH_2Cl_2. A drop of TMS (internal lock signal) and, for *N,N*-dimethylamides, cyclopentane (resolution standard) were added. For **2** and **5** a ^{13}C satellite of CH_2Cl_2 was used as a resolution standard. The CW ^1H NMR spectra were recorded on a Tesla BS-487C spectrometer at 80 MHz at the Department of Pharmacy, School of Medicine, Warsaw, with a sweep rate of 0.4 Hz s^{-1} and a sweep scale of 0.2 Hz mm^{-1}. The temperatures were measured with a methanol sample. The spectra were digitized by a semiautomatic plot reader connected to an ODRA 1305 computer. Every spectrum was represented by at least 100 points, measured with a precision of 0.1 mm. The iterative total line shape analysis was performed using the ASESIT[8] program.

The dynamic spectra of the methyl groups of *N,N*-dimethylamides were treated in the analysis as an $A \rightleftharpoons B$ spin system, and those of *N,N*-diisopropylamides as an AB part of an $AX \rightleftharpoons BY$ spin system. The determination of the enantiomerization rates (**2** and **5**) was based on the analysis of the upfield isopropyl methyl signals. The $\Delta G^{\neq}$ values in Table 1 were determined on the basis of at least three independent measurements, and the errors in the $\Delta G^{\neq}$ values were smaller than 1 kJ mol^{-1}.

RESULTS AND DISCUSSION

In the ^1H NMR spectra of *N,N*-dimethylamides **1**, **3** and **4** measured at room temperature, the signals of the *N*-methyl groups have the form of a pair of equally intense singlets which can be assigned to the methyl groups in the *E* and *Z* configurations. This pattern does not change when the temperature is lowered, and none of the investigated compounds, including **1**, show any additional signals in the *N*-methyl region at temperatures down to −70 °C. When a solution of **1** was exposed to air for a sufficiently long period, however, an additional pair of *N*-CH_3 singlets appeared in the spectrum. These signals originate from the disulphide **4**, an oxidation product of **1**; this was proved by measuring the NMR spectra of partially oxidized **1** with different amounts of independently synthesized **4** and by TLC. This observation could partly explain the discrepancy between our spectra of **1** and those reported by Fong.[3] The lack of chemical shift values in Ref. 3 makes it impossible to decide whether this is the real reason for the disagreement.

At higher temperatures the *N*-Me signals of the *N,N*-dimethylamides undergo characteristic dynamic changes, and coalesce above 50 °C owing to the increased rate of amide rotation. A comment should be made on a discrepancy between our results and those of Mires *et al.*[1] They observed the averaged *N*-CH_3 signal at 35 °C, which might be attributed to the lower nominal frequency of the spectrometer (60 MHz), some inaccuracy in the temperature determination and/or the catalytic influence of traces of DCl (from $CDCl_3$ decomposition) on the amide rotation.[9] In the diisopropylamides **2** and **5** the room temperature spectra are dynamically broadened. At 15 °C the *C*-CH_3 groups give a pair of doublets, expected for slow amide rotation. The amide rotation rates were obtained and the free energies of activation for this process were calculated on the basis of the total line shape analysis[8] of the dynamic NMR spectra of **1–5**. Table 1 shows that the barriers for the *o*-mercapto compound **1** are of very similar height to those for **3** and **4**, despite the inability of the latter to form intramolecular hydrogen bonds. The same is true for the isopropyl analogues **2** and **5**. This observation will be commented on below, together with the results of other measurements. Moreover, all the barriers for **1–5** are lower than those for other *o*-substituted benzamides,[2,9–12] excluding 2-hydroxy and 2-amino derivatives which can form relatively strong intramolecular hydrogen bonds.[2,9,10,13,14] Such a lowering of the barrier height in the investigated compounds could not be rationalized on the basis of substituent effects such as inductive (σ_I), resonance (σ_R) or steric (r_W) effects as proposed by Charton[15] (Table 2). A comparison of the magnitudes of the substituent parameters for OCH_3, SCH_3 and Cl, as well as the calculation of $\Delta G^{\neq}$ for **3** based on the linear correlation derived by Fong *et al.*,[11] suggests the barrier to amide rotation to be about 80 kJ mol^{-1}. Such an estimate of $\Delta G^{\neq}$ is, however, in definite disagreement with the experimental value (Table 2). The sulphur substituent effect is even stronger in the case of a disulphide, as shown by the comparison of the barriers for **3** and **4**.

It is difficult to specify the type of interaction causing this effect. It is possible, for example, that the sulphur electrons can stabilize the electron deficiency on the carbonyl carbon by providing competition for p–π conjugation. This mechanism would be similar to that proposed for the rationalization of the lowering of the amide rotation barrier for *N,N*-dimethyl-

Table 1. Barriers to amide rotation, $\Delta G^{\neq}$

Compound	$\Delta G^{\neq}$ (kJ mol^{-1})	Mean temperature of measurements (K)	Solvent
1	69.7	316	$CDCl_3$
	68.1	312	Pyridine
2	64.8	305	CH_2Cl_2
3	72.7	330	$CDCl_3$
	71.3	330	Pyridine
4	68.8	324	$CDCl_3$
	67.6	320	Pyridine
5	65.3	300	CH_2Cl_2

Table 2. Substituent parameters and experimental barriers to amide rotation (kJ mol^{-1}) for 2-methoxy-, 2-methylthio- and 2-chloro-*N,N*-dimethylbenzamides

Ortho substituent	I[a]	R[a]	r_W[b]	$\Delta G^{\neq}$	T (K)	Solvent
OCH_3	0.27	−0.61	1.52	75.5[c]	298	CH_3CN
SCH_3	0.23	−0.32	1.80	71.3	330	Pyridine
Cl	0.46	−0.23	1.75	80.0[d]	373	CD_3CN

[a] From Ref. 16.
[b] Van der Waals radii from Ref. 17.
[c] From Ref. 9.
[d] From Ref. 11.

benzamide in CS_2 used as a solvent.[9] The other factor which might be taken into consideration is the high polarizability of sulphur. Hence, despite the larger volume of the *ortho* substituent, coplanarity of the carbonyl group and the aromatic ring would be easier to achieve than for other substituents of similar size. As a result, the molecule could be better stabilized in the transition state of the amide rotation.[9,10,12] One should also take into account the C=O···S attraction, the occurrence of which was considered in the literature[18] for similar systems.

Another factor which deserves comment is the lowering of the $\Delta G^{\neq}$ value when the *N*-substituents are changed from methyl to isopropyl groups (Table 1). A similar observation was made for appropriate benzamides,[19] 1-naphthamides[20] and also a series of amides of aliphatic acids.[21] This effect can be attributed to the steric destabilization of the ground state of the molecule by larger *N*-substituents.[10,12,21–25] In order to elucidate the influence of intramolecular hydrogen bonding on the conformation and dynamics of *o*-mercapto-*N,N*-dialkylbenzamides, we measured the spectra of **1** and **2** in pyridine. Characteristic changes of the chemical shift of the SH protons from 3.75 and 3.78 ppm in $CDCl_3$ to 4.79 and 4.95 ppm in pyridine for **1** and **2**, respectively, show that pyridine, as well as DMSO,[1] breaks the intramolecular hydrogen bond in **1** and **2**. One observes only a small decrease, however, of the rotational barrier for **1**, similar to that for **3** and **4** (Table 1). Hence, in contrast to *o*-hydroxybenzamides[2,13,26] and *o*-hydroxythiobenzamides,[27,28] where large increases of the barrier were observed, the breaking of the intramolecular hydrogen bond in *o*-mercapto compounds hardly affects the amide rotation barrier.

The second effect of pyridine, observed for *o*-hydroxy-*N,N*-dimethylbenzamide and absent in the case of **1**, are the large changes in chemical shifts of the *N*-CH_3 groups caused by a change of conformation of the molecule. In the case of *N,N*-dimethylsalicylamide, it was observed that a strong intramolecular hydrogen bond results in a nearly coplanar conformation of the molecule, and the singlet of the methyl group in the *E* configuration is further downfield than that of the *Z*-methyl group.[13] In pyridine solution, the ordering of the *E*- and *Z*-methyl group signals is reversed, and it is similar to other *N,N*-dimethylbenzamides which do not form a chelate hydrogen bond. Benzene dilution experiments[29] for **1** and **4** show that in both cases, in $CDCl_3$, the upfield *N*-methyl singlet should be assigned to the *E*-methyl group. If we adopt the idea that the chemical shift difference between the *E*- and *Z*-methyl groups in *N,N*-dimethylbenzamides reflects the degree of twisting of the amide group from the plane of the aromatic ring,[9,11] we can conclude that the conformations of **1**, **3** and **4** are similar, and are only slightly affected by solvents such as CCl_4, $CDCl_3$ and pyridine. The above observations lead us to conclude that the intramolecular hydrogen bond in **1** and **2** is weak, and has no tendency to flatten the molecule, even in the transition state of the amide rotation.

These conclusions are further supported by the results concerning the rotation about the carbonyl—aryl bond in **2** and **5**. In the low-temperature spectra of these compounds one observes broadening, and then splitting of the isopropylmethyl doublets, which form four equally intense doublets at −40 °C. We attributed this phenomenon to restricted rotation about the carbonyl—aryl bond, similar to analogous cases.[4,26,28,30] Rotation in this case means the transition between two enantiomeric non-coplanar conformers, rather than the full rotation process. An alternative explanation of the observed splitting based on restricted rotation about the $(CH_3)_2CH$—N bond seems to be less probable, in view of the equal intensity of all observed methyl signals. It is difficult to decide whether, under the applied conditions, the rotation of the two isopropyl groups is restricted or not. However, according to Berg and Pettersson,[31] *N,N*-diisopropylbenzamide exists almost exclusively as one conformer, namely that in which the isopropylmethyl groups are arranged symmetrically with respect to the amide plane. Under conditions of rapid carbonyl–aryl rotation, such a conformer would not cause any splitting in the spectra. In the case of **5** (and **4**), restricted rotation about the S—S bond should also be considered. However, the pattern of the methyl region of the spectra, and the close similarity of the spectra of **2** and **5** (or **1** and **4**), allow the exclusion of this process. Under the conditions of restricted carbonyl–aryl rotation, disulphides **4** and **5** may form achiral and racemic diastereomers, but the spectra do not provide any evidence for this. The total line shape analysis of the dynamic spectra of isopropylamides **2** and **5**, measured below 10 °C, gave the rotation rates and the following barriers to carbonyl–aryl rotation: $\Delta G^{\neq}_{268} = 60.0$ kJ mol^{-1} for **2** and $\Delta^{\neq}_{254} = 56$ kJ mol^{-1} for **5**.

Because systematic data concerning the influence of *ortho* and *N* substituents on the carbonyl–aryl rotation in benzamides are not available in the literature, discussion of the absolute values of the determined barriers for **2** and **5** would be premature. Nevertheless, one might expect, by analogy with the situation in *o*-hydroxy-benzamides and thiobenzamides, that the intramolecular hydrogen bond should strongly reduce the barrier of this process.[4,26,28] On the contrary, however, the enantiomerization barrier for **2** is higher than that for **5**. The geometry of the transition state of this process must be deduced in order to allow any conclusions from this experimental result. Since the amide rotation is much slower than the enantiomerization, the amide moiety is approximately planar during the latter process. One can imagine two transition states of the molecule in which the amide and aromatic moieties are coplanar. On consideration of steric factors, the arrangement with the carbonyl oxygen pointing towards sulphur would seem to be energetically favourable. Hence, in the case of **2**, enantiomerization could occur without breaking the intramolecular hydrogen bond. The fact that the barrier for **2** is higher than that for **5** could lead to the conclusion that the hydrogen bond is weaker in the transition than in the ground state of enantiomerization. This need not be true, however, because the polarizability of the *ortho* substituents must be taken into account. A more polarizable S—S substituent destabilizes the transition state to a lesser extent than does SH.

In summary, our study shows that amide **1** does not form more than one species in solution, distinguishable by NMR at the applied temperatures. The intramolecular hydrogen bond between *o*-mercapto and carbonyl groups in **1** and **2** is very weak, and in the ground state the amide moiety is twisted relative to the aromatic plane. The effect of *ortho* substituents such as SH, SCH_3 or S—SR on the dynamics of the *N,N*-dialkylamide moiety is unusual in comparison with other substituents. A complete explanation for this effect demands further investigations.

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