Tetrahedron. Vol. 31, pp. 207 to 215. Pergamon Press 1975. Printed in Great Britain

RESTRICTED ROTATION IN AMIDES—VI[a]

CONFIGURATIONS AND CONFORMATIONS OF UNSYMMETRICAL TERTIARY BENZAMIDES

A. H. LEWIN,* M. FRUCHT† and K. V. J. CHEN‡
Department of Chemistry, Polytechnic Institute of New York 333 Jay Street, Brooklyn, N.Y. 11201

and

E. BENEDETTI and B. DI BLASIO
Istituto Chimico, Universita di Napoli Via Mezzocannone 4, 80134 Napoli, Italia

(*Received in the USA* 20 *June* 1974; *Received in the UK for publication* 30 *September* 1974)

Abstract—Configurational assignments in a series of N-alkyl-N-benzylbenzamides using a variety of NMR techniques lead to consistent assignments in amides with two isomers but are inconclusive for amides with single isomers. Single crystal X-ray structure determination shows the configuration of *o*-bromo-N-benzyl-N-t-butylbenzamide to have the t-Bu group *syn* to the carbonyl oxygen. Surprisingly, the major isomer of *o*-chloro-N-benzyl-N-i-propylbenzamide, appears to have the opposite configuration, *i.e.*, the i-Pr group is *anti* to the carbonyl oxygen. The structural details of *o*-bromo-N-benzyl-N-t-butylbenzamide reveal slight deviation from planarity for the amide group and chirality of the benzoyl group.

INTRODUCTION

The structure, the configurations and the conformations of amides have been a subject of continued interest for several decades. It is well known that rotation around the acyl-to-nitrogen bond is restricted, leading to the existence of two geometric isomers. These isomers are usually not separable due to the relatively low barrier to rotation (20 kcal/mole[1]); however, isomer separation has been reported for isolated cases.[2] Restricted rotation around the amide bond could be indicative of trigonal hybridization of nitrogen, with continuous overlap of the orbitals between nitrogen and the carbonyl group. On the other hand, it has been suggested that such a conclusion would be incorrect, since partial double bond character could result from overlap of the filled sp^3 orbital on nitrogen with the empty p orbital on the carbonyl carbon.[3] Microwave measurements on gaseous formamide indicate that nitrogen is a flattened pyramid[4] and X-ray crystal structure determinations of various amides indicate that the amide nitrogen is planar, or very nearly so.[5] For tertiary amides it is observed that the barrier to rotation decreases with the bulk of the substituents,[3] either on carbon or on nitrogen, and this has been interpreted as a manifestation of increased energy of the "nearly planar" ground state due to steric interactions.[3] For amides with t-Bu groups, usually only one isomer can be detected,[6,7] *e.g.*, by NMR spectroscopy, and it has been suggested that this is, in fact, due to extremely low rotational barriers, and therefore rapid rotation, resulting in averaging of the NMR signal.[7] In N - t - butyl - N - methylformamide, however, the barrier must be significant, since two amide isomers are observed by NMR.[6]

In amides with phenyl substituents on nitrogen, restricted rotation around the benzene - to - nitrogen bond has been demonstrated.[8] It has also been shown that a conformation in which the phenyl ring is turned out of the amide plane may result when the benzene ring is unsymmetrically substituted with *ortho* groups.[9] An analogous situation appears to obtain in benzamides. Thus, Jackman *et al.*[10] have found that *ortho*-substituted benzamides exhibited barriers to rotation which were considerably higher than those for any *meta* or *para* substituted benzamides and which did not correlate with substituent constants. This was attributed to steric inhibition of conjugation between the phenyl ring and the CO group, which, in this cross-conjugated system, would lead to increased resonance donation by the amide nitrogen. Restricted rotation around the benzene - to - carbonyl bond coupled with lack of coplanarity between the benzoyl phenyl and the amide linkage has also been proposed to account for the observed geminal chemical shift non-equivalence observed for the benzyl methylene protons in unsymmetrically *ortho*-substituted N,N - dibenzylbenzamides.[11]

The isomer composition of tertiary amides with different substituents on nitrogen has been investigated and a general conclusion, that with the exception of formamides, the bulkier of the two groups on nitrogen would be *syn* to the carbonyl oxygen in the major isomer, was reached.[6]

In the course of our investigations of amides, and in

[a]Part V: A. H. Lewin and C. P. Talley, submitted to *J. Am. Chem. Soc.*

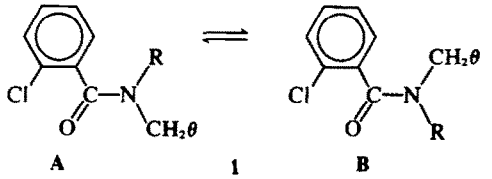
†Taken in part from the dissertation of M. Frucht, submitted to the Faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry (1973).

‡Taken in part from the thesis of K. V. J. Chen, submitted to the Faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Master of Science in Chemistry (1972).

particular benzamides, we have examined a series of N - alkyl - N - benzyl - *ortho* - substituted benzamides and have found, to our surprise, an apparent exception to this generalization. We have, therefore, carried out a single crystal X-ray structure determination of one of the key amides and our results have some bearing on the general question of the structure, conformation and configurational composition of amides.

RESULTS

Examination of a series of *o* - chloro - N - alkyl - N - benzylbenzamides (**1**) by NMR has revealed the doubling of all the signals, due to the presence of the two amide isomers (**A** and **B**), in all cases except one. Thus, for example, for *o* - chloro - N - benzyl - N - methylbenzamide (**1a**) two singlets (δ 4·32, 4·77) were observed for the N-Me group and two sets of signals were associated with the benzyl methylene hydrogens. The methylene signals appeared as two AB quartets due to geminal nonequivalence within each methylene group, arising from chirality of the *o*-chlorophenyl group and slow rotation around the phenyl - to - carbonyl bond.[11] An analogous situation obtains when the Me group is replaced by an ethyl (**1b**) or i-Pr (**1c**) group. Only one set of signals is observed, however, for R = t-butyl (**1d**), down to −60°, at 220 MHz.



a: R = Me
b: R = Et
c: R = $CHMe_2$
d: R = CMe_3

Isomer identification

Resonance assignments, *i.e.*, isomer identifications, were done using several methods.

Chemical shift comparisons. The chemical shifts of the benzyl methylene signals of numerous substituted N,N - dibenzylbenzamides have been found to be very similar (Table 1). It therefore seemed reasonable to attempt to assign the resonances by extrapolation from *m* - dinitro - N,N - dibenzylbenzamide, for which resonance assignments had been made by the NOE.[12] Using the data in Table 2 and making such an extrapolation, leads to the assignment of the downfield methylene resonance to isomer **A** and the upfield resonance to isomer **B** for **1a–c**. However, the configurational assignment of **1d**, whose resonance has an intermediate chemical shift value (Table 2), remains unresolved.

Geminal magnetic non-equivalence. We had found that in *o* - substituted - N,N - dibenzylbenzamides both benzyl methylene groups exhibit geminal non-equivalence.[11,12] The chemical shift difference between the geminal protons of the methylene group *syn* to the carbonyl oxygen (downfield) was found to be larger than that for the *anti* methylene protons (upfield).[12] For the benzamides under investigation, geminal non-equivalence was observed, as expected (Table 3). Using the empirical generalization that a smaller chemical shift non-equivalence is associated with an *anti* methylene group in these system,[13] assignments can be made for amides **1a–c**, which are consistent with those made by chemical shift comparisons (*vide supra*). The configuration assigned to *o* - chloro - N - benzyl - N - t - butylbenzamide (**d**) by this method would involve an *anti* methylene group, *i.e.*, isomer **B**.

Solvent shifts. Resonance assignment using aromatic - solvent - induced shift (ASIS) has been successful when both amide isomers are observable by NMR.[14] Our results (Table 4) for the N - methyl - (**1a**), N–Et (**1b**) and N - i - Pr (**1c**) amides confirm the assignments made using other

Table 1. Chemical shifts of N-benzyl methylene protons in substituted N,N-dibenzylbenzamides[a]

Benzoyl substitution	Chemical shift, δ (ppm)	
H[b]	4·36	4·70
o-Me	4·25	4·74
o-NO_2	4·22	4·76
p-NO_2	4·38	4·68
o-F	4·30	4·68
2,4-$(OMe)_2$	4·26	4·72
2,6-$(OMe)_2$	4·22	4·73
2,6-Cl_2	4·23	4·72
2-Cl-6-NO_2	4·25	4·79

[a] In $CDCl_3$ at 34°.
[b] 10°.

Table 2. Chemical shifts of N - benzyl methylene protons in *o* - chloro - N - alkyl - N - benzylbenzamides (**1**)[a]

1. Alkyl	Chemical shift, δ (ppm)	
a Me	4·32	4·77
b Et	4·35	4·78
c $CHMe_2$	4·30	4·85
d CMe_3	4·51	

[a] In $CDCl_3$ at 34°.

Table 3. Chemical shift non-equivalence of benzyllic geminal methylene protons in *o* - chloro - N - alkyl - N - benzylbenzamides[a]

1. Alkyl	Chemical shift non-equivalence, (ν_{AB}), ppm	
a Me	0·20	0·15
b Et	0·30	0·07
c i-Pr	0·24	0·00
d t-Bu	0·12	

[a] In CCl_4 at 0°.

Table 4. Aromatic - solvent - induced - shifts of the N - benzyl methylene protons of *o* - chloro - N - alkyl - N - benzylbenzamides

1. Alkyl	Chemical shift, δ (ppm), in benzene $CDCl_3$	Benzene	$\Delta\delta$[a]
a Me	4·32	4·11	0·21
	4·77	4·68	0·09
b Et	4·35	4·04	0·31
	4·78	4·69	0·09
c $CHMe_2$	4·30	4·06	0·24
	4·85	4·69	0·16

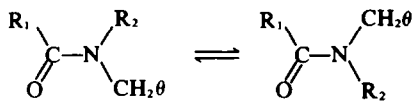
[a] $\delta_{CDCl_3} - \delta_{\phi H}$.

methods, namely, that the isomer with the downfield methylene group has configuration A since it exhibits the smaller upfield ASIS. No conclusions can be drawn for the N - t - butyl amide.

Lanthanide induced shifts. It has been demonstrated that lanthanide induced shifts provide a simple and unambiguous method for resonance assignment in amides when signals for both amide isomers are observable.[15] We applied this approach to the amides under investigation and attempted to predict the induced shift for *o* - chloro - N - benzyl - N - t - butylbenzamide (**1d**) using model compounds.

The LIS values for the benzyl methylene protons in the four amides under investigation were determined under identical conditions in the hope that conclusions could be drawn regarding the configuration of the single isomer observed for **1d** (Table 5). The results confirm the assignments for **1a–c** but are quite ambiguous for **1d**. When compared with **1a, b** it would seem that the configuration of **1d** resembles **A** but comparison with **1c** leads to the opposite conclusion.

The LIS values of the benzyl methylene hydrogens in a series of N - alkyl - N - benzylformamides (**2**) and acetamides (**3**) were determined (Table 6). Resonance assignments for N - benzyl - N - methyl formamide **2a** and acetamide **3a** had been previously made by the NOE.[16] The configurational assignments for **2b–d** and **3b, c** were made using the LIS method,[14] *i.e.*, the benzyl methylene hydrogens which experienced the larger LIS (Table 6) were assigned to the isomer with configuration **A**. Configuration **B** was assigned to **3d** on the basis of the similarity of its LIS value to the **B** isomer of **3c**.



A **B**

2: $R_1 = H$ **3**: $R_2 = Me$

a: $R_2 = CH_3$
b: $R_2 = Et$
c: $R_2 = CHMe_2$
d: $R_2 = CMe_3$
e: $R_2 = CH_2\phi$

Table 5. $Eu(DPM)_3$ induced shifts of benzyl methylene protons in *o* - chloro - N - alkyl - N - benzylbenzamides[a]

1. Alkyl	Induced shift, Hz[b,c,d]	
a Me	126	88
b Et	118	88
c $CHMe_2$	139	120
d CMe_3	111·5	

[a] In CCl_4 at 0°.
[b] At 220 MHz.
[c] Due to geminal non-equivalence each methylene group appeared as an AB quartet; the reported shift represents the induced shift of the center of the quartet.
[d] Eu/Amide = 0·05.

Table 6. $Eu(DPM)_3$ induced shifts of benzyl methylene protons in N - alkyl - N - benzylformamides and acetamides[a]

Compound	Induced shift, Hz[b,c] in isomer A	B
2a N-benzyl-N-methylformamide	286	87
2c N-benzyl-N-i-propylformamide	182	50
2d N-benzyl-N-t-butylformamide	173	65
3a N-benzyl-N-methylacetamide	185	86
3b N-benzyl-N-ethylacetamide	179	88
3c N-benzyl-N-i-propylacetamide	172	112
3d N-benzyl-N-t-butylacetamide		124

[a] In CCl_4 at 0°.
[b] At 220 MHz.
[c] Eu/Amide = 0·05.

The similarity in the LIS values for N - benzyl - N - t - butylacetamide and *o* - chloro - N - benzyl - N - t - butylbenzamide (**1d**) suggests configuration **B** for **1d**. However, the large, seemingly random, variations in the LIS values must make this conclusion rather tentative.

A further attempt to establish the configuration of **1d** was made by comparing LIS values for the *syn* and *anti* benzyl methylene hydrogens of N,N - dibenzylformamide (**2e**) and acetamide (**3e**) with the LIS of the analogous hydrogens in **1d** (Table 7). The *syn* and *anti* resonances in **2e** and **3e** had been assigned by the NOE[15] and, as

Table 7. $Eu(DPM)_3$ induced shifts of benzyl methylene protons[a]

Compound	Induced shift, Hz[b,c] *syn*[d]	*anti*[b]
N,N-dibenzylformamide	68	39
N,N-dibenzylacetamide	67	38
o-chloro-N-benzyl-N-t-butylbenzamide		41·5

[a] In CCl_4.
[b] At 60 MHz at 34°.
[c] Eu/Amide = 0·1.
[d] Relative to carbonyl oxygen.

expected, the relative LIS values were found to be consistent with those assignments. Inspection of Table 7 suggests configuration **B** for **1d** on the basis of the similarity of its LIS value with those of the *anti* methylene hydrogens.

Single crystal structure determination. In order to obtain additional information about the configuration of **1d**, the analogous (but somewhat higher melting) *o* - bromo - N - benzyl - N - t - butylbenzamide (**4**) was prepared and subjected to structure determination by X-ray. The molecular model of **4**, with its geometry, is shown in Fig 1. Bond angles and lengths are all close to normal values, within experimental error. For example, the C(10)-Br distance (1·894 ± 0·014 Å) is in good agreement with the expectation value for the $Br–C_{aromatic}$ linkage, namely, 1·8966 ± 0·0019 Å, recently calculated from a survey[17] of 60 such bond distances between monovalent Br atoms and C atoms in an aromatic ring.

The amide group deviates slightly from planarity; the mean square distance of the 6 atoms from the best plane passing through them is 0·003 Å. The angle between the mean planes of the amide and the benzoyl phenyl is 79°; the angle between the amide and the benzoyl phenyl group is 84°. Furthermore, the two phenyl groups are nearly orthogonal (87°).

The solid state data clearly indicate that the molecule is configurationally and conformationally frozen as far as motion of the groups is concerned. The configuration about nitrogen is such that the bulky t-Bu substituents is *syn* to the carbonyl O atom and the benzyl group is *anti* with respect to it. Some of the shortest intramolecular distances are shown in Fig 2; the mode of packing of the molecules as viewed along the *b* axis along with the shortest intermolecular contacts, is shown in Fig 3.

Isomer composition

The isomer compositions of *o* - chloro - N - alkyl - N - benzyl benzamides (**1a–d**), as well as those of N-alkyl-N-benzylformamides and acetamides, were determined in carbontetrachloride solution, at 0°, by integration of the NMR signals (Table 8). The results are based on the resonance assignments described and on the X-ray crystal structure determination of *o* - bromo - N - benzyl - N - t - butylbenzamide.

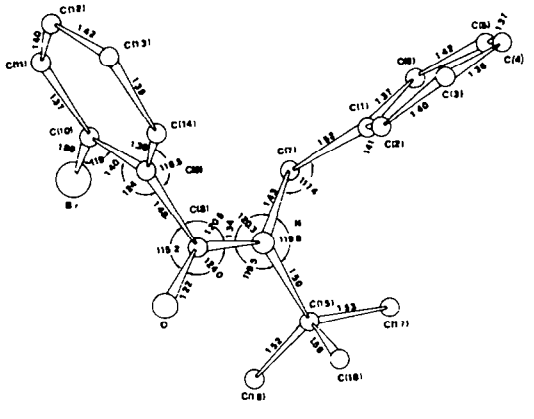


Fig 1. Molecular model of *o*-bromo-N-benzyl-N-t-butylbenzamide as viewed along the *c* and *b* axes (A and B, respectively). Bond distances (±0·02 Å) and bond angles (±0·6°) are reported.

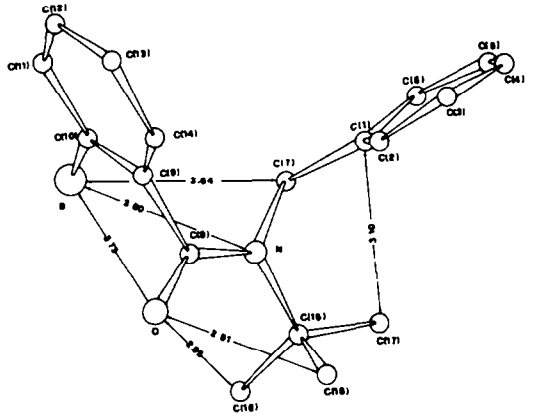


Fig 2. Molecular model of *o*-bromo-N-benzyl-N-t-butylbenzamide. The shortest intramolecular distances are indicated.

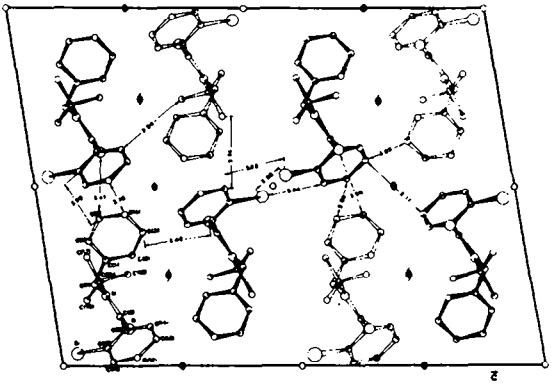


Fig. 3. Mode of packing of *o*-bromo-N-benzyl-N-t-butylbenzamide molecules as viewed along the *b* axis. Some of the shortest intermolecular contacts are reported.

Table 8. Composition of N - alkyl - N - benzyl amides[a]

Compound R	R′	% Composition[b]	
		A	B
2a Me	H	46	54
2b Et	H	44	56
2c $CHMe_2$	H	65	35
2d CMe_3	H	89	11
3a Me	CH_3	69	31
3b Et	CH_3	55	45
3c $CHMe_2$	CH_3	37	63
3d CMe_3	CH_3	0	100
1a Me	*o*-C_6H_4Cl	55	45
1b Et	*o*-C_6H_4Cl	63	37
1c $CHMe_2$	*o*-C_6H_4Cl	70	30
1d CMe_3	*o*-C_6H_4Cl	0	100

[a] By integration of NMR (220 MHz) signals in CCl_4 at 0°.
[b] A refers to configuration with benzyl *syn* to carbonyl oxygen.

DISCUSSION

All attempts to pinpoint the configuration of *o* - chloro - N - benzyl - N - t - butylbenzamide (**1d**), in solution have proven to be inconclusive. The observation of a chemical shift value for the benzyl methylene protons of **1d** intermediate between those observed for the benzyl methylene protons in isomers **A** and **B** for the amides **1a–c**, could be interpreted as being due to rapid rotation around the amide bond. Thus, if isomers **A** and **B** were approximately equally populated in **1d**, rapid rotation would lead to an average chemical shift value. Rapid rotation has, in fact, been proposed to account for the observation of a single isomer in the analogous amide, *o* - methyl - N - benzyl - N - t - butylbenzamide.[7] Since no signal broadening was observed by us down to −60° at 220 MHz, this interpretation would require that the amide rotational barrier be extremely low (6 kcal/mole), which would seem quite unlikely. Furthermore, it should be noted that the N-benzyl methylene protons of *o*-chloro-N - benzyl - N - t - butylbenzamide (**1d**) appear as an AB quartet, *i.e.*, are non-equivalent, and therefore, rotation around the *o* - chlorophenyl - to - carbonyl carbon–carbon bond must be slow, on the NMR time scale, already at 20°.[11] It seems highly improbable that the barrier to rotation around the carbonyl - to - nitrogen amide bond would be smaller than the phenyl - to - carbonyl rotational barrier.

Resonance assignments using the LIS[15] are certainly not straightforward in amides exhibiting only one isomer. Comparison of the magnitude of the LIS is empirical, since equilibrium constants undoubtedly vary from system to system and the specific pseudo contact terms are not necessarily invariant. In fact, inspection of Tables 5 and 6 suggests that further investigation of the factors influencing the magnitude of the LIS is necessary. It therefore appears that the only useful information for resonance assignment, in this case, is the magnitude of the chemical shift non-equivalence. We have shown that the extreme downfield shift of one of the protons of the benzyl methylene *syn* to the carbonyl oxygen is due, at least in part, to the existence of a preferred conformation in which the C–H bond is coplanar with and parallel to the C=O bond.[15] Such a conformation for the *syn* methylene group is encouraged by the presence of a bulky *anti* group and therefore, if **1d** had configuration **A**, a large chemical shift non-equivalence of the benzyl methylene protons should have been observed. The small non-equivalence observed is thus perfectly consistent with the existence of a single amide isomer for **1d** with configuration **B**.

The solid state data for *o* - bromo - N - benzyl - N - t - butylbenzamide (**4**) support this conclusion; they reveal the presence of a single isomer of configuration **B**. Although solid state and solution configurations do not necessarily correspond, it appears to be highly unlikely that only one isomer would be observed in the solid and *only* the other isomer would be observed by NMR in solvents of varying polarity and over a temperature range.* In the solid, the t-Bu group adopts a conformation by which the Me groups minimize the contacts with the oxygen; they are almost staggered with respect to the C′–N bond. However, two $CH_3 \ldots O$ distances (2·93 and 2·95 Å) and the C(1)...C(2) distance (3·10 Å) present smaller values than the sum of the van der Waals radii for the atoms and groups involved.[18] On the other hand, a conformation for the molecule in which the two substituents at the nitrogen are interchanged would produce better contacts with the oxygen but would also give rise to even smaller contacts between the Me groups and the C atoms of the benzoyl phenyl. Instead, in the conformation experimentally found, the intramolecular contacts of the atoms of the benzoyl phenyl are all within the expectation values. Since an essentially "frozen out" conformation is observed in the solid state, it would seem likely that a relatively high barrier to isomerization around the carbonyl - to - nitrogen bond exists in solution.

Isomer identifications for the amides **1a–c**, on the other hand, were straightforward. All the methods applied lead to the same configurational assignments to the major and minor isomers and herein lies the surprise. If the resonance assignments are correct, then it appears that as the bulk of the alkyl group increases, *i.e.*, Me < Et < i-Pr, the stability of isomer **A** relative to isomer **B** increases as well. In other words, the bulky group evidently prefers the position *syn* to the *o*-chlorophenyl group to the position *syn* to the carbonyl oxygen. This is contrary to the situation in acetamides and, furthermore, apparently does not hold for a t-Bu group. Thus, whereas there is a smooth increase in the percentage of isomer **B** as the N-alkyl group is changed through the series Me, Et, i-Pr and t-Bu for N - alkyl - N - benzylacetamides, the opposite trend is observed for *o* - chloro - N - alkyl - N - benzylbenzamides (**1a–c**) with a discontinuity for the t-Bu substituted benzamide (**1d**) for which apparently only isomer **B** is detected.

A possible explanation for this unexpected behavior may be that, in fact, the resonance assignments for the amides **1a–c** are incorrect. If that were the case, no anomaly would exist in the isomer composition. Certainly, resonance assignments by comparisons of chemical shift values and of magnitudes of geminal non-equivalences of the N-benzyl methylene groups are empirical and therefore tenuous. Shifts induced by aromatic solvents have also been found to give erroneous results[19] in some cases and it is conceivable that these might lead to the wrong assignments. The observed LIS might be misleading, as well. Since the magnitude of the LIS is a function of the equilibrium constant of the lanthanide-substrate complex, among other things, it could well be that one of the amide isomers would preferentially complex with the lanthanide shift reagent. Therefore, if the complexing ability of isomer **A** exceeded that of isomer **B** it might be possible that although the distance between the lanthanide ion and the benzyl methylene group in isomer **B** exceeds that in isomer **A**, the actual observed LIS for isomer **A** would exceed that for isomer **B**. Thus, it is possible that our isomer identifications are incorrect; it seems unlikely, however, that *every* method leads to incorrect assignments. We feel, therefore, that our assignments are

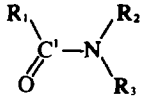
*The NMR characteristics of **4** and **1d** are essentially identical.

probably correct and we will continue to investigate the causes for the unexpected isomer composition observed.

The crystal structure of *o* - bromo - N - benzyl - N - t - butylbenzamide conforms well to the expected structure of *o*-substituted benzamides in that it clearly demonstrates the chirality of the benzoyl phenyl with respect to the plane of the CO group. In fact, in this case, the two phanes are at an angle of 79° to each other.

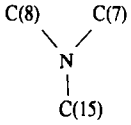
Thus, in the solid, there is no conjugation possible in the benzoyl group. It is also evident from the X-ray data that coplanarity of the benzoyl phenyl with the mean amide plane would lead to severe van der Waals interactions; in fact, even in the preferred conformation in the solid state, the Br-C(7) distance is smaller than the sum of the van der Waals radii for Br and an Me group. It is therefore easy to accept the observed barrier to rotation and chirality around the phenyl-to-carbonyl bond.

The amide group was found to be slightly non-planar. As has recently been pointed out[20] at least two mechanisms are effective in determining the non-planarity of the amide group: torsion around the C'–N bond and the non-planar hybridization of the nitrogen (the contribution from out-of-plane bending at the carbonyl carbon being smaller).



$\omega_1 = R_1C'NR_3$: $\omega_3 = OC'NR_3$
$\omega_2 = OC'NR_2$ $\omega_4 = R_1C'NR_2$

The non-planar hybridization of the nitrogen, measured by $|\omega_1 - \omega_4 - 180°|$ seems to have a greater weight when larger deviations from planarity are required. In the present structure $|\omega_1 - \omega_4 - 180°| = 6°$. For the group



the deviations of the single atoms from the mean square plane in angstoms are the following: C(7) −0·012, C(8) −0·013, C(15) −0·011, N +0·036, confirming the non-planar hybridization of the nitrogen. Although the equilibrium conformation of the amide group may be planar or close to it, out of plane deformation can evidently be made at very low energy cost.

Examination of the isomer compositions for formamides and acetamides in Table 8 suggests a possible ordering of groups by "size", namely, if the reasonable assumption that the carbonyl oxygen is "larger" than the formyl hydrogen is made, then it follows that since isomer **B** is the major isomer in **2c**, a benzyl group is larger than a Me group. Similarly, a benzyl group is larger than an Et group, but is smaller than either an i-Pr or a t-Bu group. Analogously, if the assumption is made that methyl is larger than the carbonyl oxygen, the same size sequence is obtained. These observations are stated in terms of free energy differences between **A** and **B** in Table 9 and can also be summarized as

$$H < O < Me < Et < CH_2\phi < CHMe_2 < CMe_3.$$

This size sequence is obviously violated in the *o*-chlorobenzamides where it appears that $CH_2\phi > CHMe_2$.

Table 9. Free energy differences between N - Benzyl - N - alkyl formamide and acetamide isomers[a]

Compound	R_1	R_2	$\Delta\Delta F$ (kcal/mole)[b]
2a	H	Me	−0·09
2b	H	Et	−0·15
2c	H	$CHMe_2$	+0·34
2d	H	CMe_3	+1·15
3a	Me	Me	+0·20
3b	Me	Et	+0·12
3c	Me	$CHMe_2$	−0·38
3d	Me	CMe_3	< −1·6

[a] From data of Table 8.
[b] $\Delta F_B - \Delta F_A$.

CONCLUSIONS

The generalization that in tertiary amides (other than formamides) with unequal substituents on nitrogen the bulky substituent preferentially occupies the position *syn* to the carbonyl oxygen evidently breaks down for *o* - chloro - N - benzyl - N - alkyl - benzamides where alkyl = Et and i-Pr.

Attempts to assign the configuration of *o* - chloro - N - benzyl - N - t - butylbenzamide, which appears to exist as a single isomer, in solution, are inconclusive but strongly suggest a configuration in which the t-Bu group is *syn* to the carbonyl oxygen. Single crystal X-ray structure determination of the *o*-bromo analog confirm this configuration in the solid state and show that the amide group is slightly non-planar. Chirality of the benzoyl-phenyl with respect to the plane of the carbonyl group, which had been postulated for *o*-substituted benzamides[10,11] is also observed in the solid state.

EXPERIMENTAL

N - *benzyl* - N - *methylformamide.* In a r.b. flask fitted with a distillation head were placed 14·9 g (0·1 mole) N - benzyl - N - methyl amine (Aldrich), 10 g (0·2 mole) formic acid (Allied) and 80 ml toluene. The soln was distilled slowly; after 2–3 h 60 ml azeotrope (b.p. 85–87°) had been collected. The residue was then transferred to a 50 ml r.b. flask equipped with a short path distillation head and distilled at reduced pressure. The portion boiling at 107–110°/4 mm was collected. The colorless liquid had $n_D^{30} = 1·544$.

N - *benzyl* - N - *ethylformamide.* The procedure described for the methyl analog was followed, starting with 16·4 g (0·1 mole) N - benzyl - N - ethylamine (Columbia) and 10 g (0·2 mole) formic acid (Allied) in 80 ml toluene. The portion boiling at 110–117°/4 mm was collected. The colorless liquid had $n_D^{30} = 1·534$. (Found: C, 73·91; H, 8·16; N, 8·69. Calcd: C, 73·62; H, 7·97; N, 8·59%).

N - *benzyl* - N - *iso* - *propylformamide.* Using 18·7 g (0·1 mole) N - benzyl - N - isopropylamine (Aldrich), 10 g (0·2 mole) formic acid (Allied) in 80 ml toluene, the procedure for the N-methyl analog was followed. The portion boiling at 105–112°/3·5 mm was

collected. The liquid had $n_D^{30} = 1.528$. (Found: C, 74·29; H, 8·56; N, 7·82. Calcd: C, 74·54; H, 8·47; N, 7·90%).

N - *benzyl* - N - *t* - *butylformamide.* The procedure described for N - benzyl - N - methyl formamide was followed using 19·1 g (0·1 mole) N - benzyl - N - t - butylamine (Ames), 10 g (0·2 mole) formic acid and 80 ml toluene. The portion boiling at 105–110°/3 mm was collected as a solid and recrystallized from pentane–ethanol to give 10·4 g of colorless needles, m.p. 39°. (Found: C, 75·50; H, 9·11; N, 7·38. Calcd: C, 75·39, H, 8·90; N, 7·33%).

N - *benzyl* - N - *methylacetamide.* A soln of 2·8 g (0·04 mole) acetyl chloride in 50 ml dry benzene was added dropwise to a stirred soln of 5·54 g (0·045 mole) N - benzyl - N - methylamine (Aldrich) and 10·1 g (0·1 mole) triethylamine (Eastman) in 200 ml dry benzene. After the addition was completed, the mixture was refluxed overnight. Workup and removal of most of the benzene on a rotary evaporator was followed by short path distillation. The portion boiling at 112–116°/4 mm was collected as a solid. Recrystallization from pentane–ethanol yielded colorless crystals, m.p. 48°. (Found: C, 73·77; H, 8·16; N, 8·72. Calcd: C, 73·62; H, 7·97; N, 8·59%).

N - *benzyl* - N - *ethylacetamide.* Starting with 12·0 g (0·076 mole) of N - benzyl - N - ethylamine (Columbia) 2·8 g (0·04 mole) acetyl chloride and 20 g (0·2 mole) triethylamine in dry benzene the procedure described for the methyl analog was followed. The portion boiling at 117–121°/4 mm was collected. The colorless liquid had $n_D^{30} = 1.532$. (Found: C, 74·53; H, 8·59; N, 7·83. Calcd: C, 74·57; H, 8·47; N, 7·90%).

N - *benzyl* - N - *i* - *propylacetamide.* Starting with 13·0 g (0·085 mole) of N - benzyl - N - i - propylamine (Aldrich), 5·6 g (0·08 mole) acetyl chloride and 10 g (0·1 mole) triethylamine in dry benzene, the procedure described for N - benzyl - N - methylacetamide was followed. The product was a colorless liquid $n_D^{30} = 1.527$. (Found: C, 73·74; H, 8·86; N, 7·36. Calcd: C, 75·39; H, 8·90; N, 7·33%).

N - *benzyl* - N - *t* - butylacetamide. The procedure described for the N-methyl analog was followed, using 13·9 g (0·085 mole) N - benzyl - N - t - butylamine (AMES), 5·6 g (0·08 mole) acetyl chloride and 20 g (0·2 mole) triethylamine in dry benzene. The product collected from short path vacuum distillatiion was recrystallized from pentane–ethanol to give colorless crystals m.p. = 73°. (Found: C, 75·99; H, 9·27; N, 5·83. Calcd: C, 76·09; H, 9·27; N, 5·83%).

o - *Chloro* - N - *benzyl* - N - *methylbenzamide.* The general procedure for acetamides was followed starting with 8·8 g (0·05 mole) *o*-chlorobenzoylchloride (Pfaltz and Bauer), 7·5 g (0·05 mole) N - benzyl - N - methylamine (Aldrich) and 10 g (0·1 mole) triethylamine in dry benzene. The oil was vacuum distilled and yielded a waxy solid, m.p. 39–43°.

o - *Chloro* - N - *benzyl* - N - *ethylbenzamide.* The general procedure described was followed using the appropriate amount of N - benzyl - N - ethylamine. The product was a liquid, coming over at 164–174/0·75 mm.

o - *Chloro* - N - *benzyl* - N - *i* - *propylbenzamide.* Following the procedure described with 10 g (0·07 mole) N - benzyl - N - i - propylamine, 5·4 g (0·03 mole) *o*-chlorobenzoyl chloride and 5 g (0·05 mole) triethylamine in dry benzene and recrystallization from pentane–ethanol, white needles m.p. 47° were obtained.

o - *Chloro* - N - *benzyl* - N - *t* - *butylbenzamide.* The general procedure was followed using 8·8 g (0·05 mole) *o*-chlorobenzoyl-chloride, 8·3 g (0·05 mole) N - benzyl - N - t - butylamine and 10 g (0·1 mole) triethylamine in dry benzene. The resulting solid was recrystallized from 80% EtOH; m.p. 73–74°.

o - *Bromo* - N - *benzyl* - N - *t* - *butylbenzamide.* The procedure followed was identical to that for the chloro analog. The product was recrystallized from 80% EtOH; m.p. 93–94·5°.

Single crystal X-ray structure determination of o - *bromo* - N - *benzyl* - N - *t* - *butylbenzamide.* Crystals of *o* - bromo - N - benzyl - N - t - butylbenzamide occur as colorless irregular prisms. Most of the specimens which were examined could be seen microscopically to present many irregularities on their surface. Attempts to improve the quality of the crystals by recrystallization from different solvent mixtures were unsuccessful. The crystals were elongated along the *b* axis. Preliminary Weissenberg and precession photographs taken with CuKα radiation indicated the following systematic absences: h k l if h+k is odd, h O l if l is odd. Together with the monoclinic lattice symmetry these suggested as possible space groups either the centrosymmetric C2/c or the acentric Cc. Cell dimensions and relative intensities were measured at room temp with Zr-filtered MoK$_\alpha$ radiation and pulse height discrimination on a Siemens automatic diffractometer. Cell dimensions were obtained from a least square fitting[21] of the angular values (θ, χ and ϕ) of twelve high angle reflections ($\theta > 30°$), measured with a narrow slit. The crystal data are reported in Table 10. The intensities were collected using θ-2θ scans with the *f* five peaks technique. The scan width was 1·0° of θ over the explored range of θ (2–60°). Two octants of reciprocal space were surveyed and 1217 reflections of the 2930 scanned had net counts above threshold. The threshold level was defined at 10% of the total background count or a net count of 100, whichever was greater. Reflections considered "unobserved" were excluded from the least-squares refinement. A standard reflection was measured after every 20 reflections to monitor any misalignment or crystal degradation which may occur. The intensity of the standard reflection had decreased about 5% at the end of data collection; this decrease was considered tolerable. The data were corrected for Lorentz and polarization factors and no absorption correction was made because of the smallness of the crystal used in the data collection (0·2 × 0·2 × 0·3 mm).

The structure was solved by the heavy-atom method. The position of the Br atom was obtained from the Harker section of a sharpened Patterson function. The coordinates of the bromine atom were refined with two cycles of full-matrix least-squares. The phases for the first Fourier synthesis were based on the structure factor calculation (disagreement index R = 0·42) from the refined position of the bromine atom. All O, N and C atoms were distinctly located in this Fourier synthesis. Seven cycles of least-squares, of which the last three were with anisotropic thermal factors, were sufficient to bring the disagreement index to 0·087 for the 1217 measured reflections. The hydrogen atoms were introduced before the last cycle in their stereochemically expected positions (d_{C-H} = 1·08 Å, C–C–H = 109·5° and 120° for H atoms bonded to tetrahedral and trigonal C atoms respectively) with an isotropic thermal factor equal to the isotropic B value of the

Table 10. Crystal Data of *o* - bromo - N - benzyl - N - t - butyl benzamide

Molecular formula	$C_{18}H_{20}NOBr$
Molecular weight	346·13 a.m.u.
Space group	C2/c
Z	8 molecules/unit cell
a	18·262 ± 0·009 Å
b	7·726 ± 0·004 Å
c	24·313 ± 0·010 Å
β	99·08 ± 0·02 Å
V	3387·6 Å^3
Density, flotation	1·34 g/cm^3
Density, calculated	1·35 g/cm^3
Radiation	MoK$_\alpha$, λ = 0·71069 Å; Zr-filtered
Temp	23°, ambient
Number of independent reflections	1217

Table 11. Final atomic parameters for *o* - bromo - N - benzyl - N - t - butyl benzamide with their estimated standard deviations*

Atom	A. Positional parameters x/a	y/b	Z/c
Br	0·0313(1)	0·2305(2)	0·0271(1)
O	0·1028(4)	−0·0478(11)	0·1492(4)
N	0·1975(5)	0·0712(12)	0·1118(4)
C(1)	0·2967(6)	0·3019(14)	0·1217(5)
C(2)	0·3102(6)	0·3030(14)	0·1805(5)
C(3)	0·3730(7)	0·3881(17)	0·2082(6)
C(4)	0·4212(7)	0·4678(17)	0·1789(6)
C(5)	0·4104(7)	0·4654(19)	0·1216(7)
C(6)	0·3463(6)	0·3810(18)	0·0929(6)
C(7)	0·2263(6)	0·2233(16)	0·0893(5)
C(8)	0·1344(6)	0·0788(15)	0·1337(5)
C(9)	0·0984(6)	0·2480(15)	0·1410(5)
C(10)	0·0500(6)	0·3313(18)	0·0989(6)
C(11)	0·0127(8)	0·4811(21)	0·1076(8)
C(12)	0·0256(9)	0·5546(21)	0·1612(9)
C(13)	0·0748(8)	0·4712(22)	0·2047(7)
C(14)	0·1096(8)	0·3169(21)	0·1943(7)
C(15)	0·2333(6)	−0·1018(16)	0·1053(5)
C(16)	0·1812(9)	−0·2191(21)	0·0668(8)
C(17)	0·3066(9)	−0·0785(22)	0·0829(9)
C(18)	0·2523(10)	−0·1909(22)	0·1637(7)
H-C(2)	0·272	0·239	0·204
H-C(3)	0·383	0·391	0·253
H-C(4)	0·469	0·534	0·201
H-C(5)	0·450	0·526	0·099
H-C(6)	0·337	0·379	0·048
H-C(11)	−0·025	0·540	0·074
H-C(12)	−0·002	0·674	0·169
H-C(13)	0·085	0·528	0·246
H-C(14)	0·145	0·251	0·228
H(1)-C(7)	0·184	0·321	0·086
H(2)-C(7)	0·234	0·191	0·048
H(1)-C(16)	0·208	−0·347	0·063
H(2)-C(16)	0·165	−0·167	0·027
H(3)-C(16)	0·132	−0·245	0·086
H(1)-C(17)	0·330	−0·204	0·078
H(2)-C(17)	0·342	0·003	0·109
H(3)-C(17)	0·292	−0·020	0·041
H(1)-C(18)	0·282	−0·312	0·160
H(2)-C(18)	0·205	−0·211	0·182
H(3)-C(18)	0·292	−0·106	0·192

carrier atoms. All the H atom parameters were kept fixed. In the final stage of the refinement process the weighting scheme suggested by Cruickshank and Pilling[22] was adopted. The final atomic coordinates and thermal parameters for all the non-hydrogen atoms are given in Table 11. A list of the observed structure factors is available as a Supplementary Publication.*

Physical measurements. NMR spectra were recorded on a Varian HR220 spectrometer with variable temp accessory. Chemical shifts were determined with the aid of TMS side bands, in the region of interest, introduced by an Electronic Resonator.

M.ps were determined on a Thomas–Hoover, Unimelt, capillary m.p. apparatus and are uncorrected.

The refractive index was measured on a Bausch and Lomb refractometer at 30°.

*This table has been deposited with the National Lending Library, England. Copies may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester, CH1, 1NZ, England.

Table 11 (*Contd.*)

B. Thermal factor (temperature factor in the form: $T = \exp -1/4(B_{11}h^2a^{*2} + B_{22}k^2b^{*2} + B_{33}l^2c^{*2} - 2B_{12}hka^*b^*2B_{13}hla^*c^* + 2B_{23}klb^*c^*)$

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Br	6·2(1)	9·3(1)	5·3(1)	−0·4(1)	−1·1(1)	1·2(1)
O	4·4(4)	3·8(4)	8·8(7)	−0·2(3)	2·1(4)	0·0(4)
N	2·9(4)	3·9(5)	4·3(5)	−0·3(4)	0·5(3)	−0·7(4)
C(1)	3·2(5)	2·6(5)	4·9(6)	0·5(4)	0·4(4)	0·3(5)
C(2)	4·0(5)	2·3(5)	4·5(5)	0·2(4)	0·7(4)	−0·6(4)
C(3)	4·3(5)	4·4(7)	5·1(7)	0·6(5)	0·1(5)	−0·6(6)
C(4)	4·1(6)	4·1(7)	7·5(9)	0·7(5)	0·3(5)	−0·8(6)
C(5)	4·5(6)	4·7(7)	8·7(10)	0·0(6)	1·2(6)	0·0(7)
C(6)	3·9(5)	4·4(7)	5·7(7)	−0·3(5)	0·8(5)	0·4(6)
C(7)	3·4(5)	4·0(6)	4·6(5)	−1·1(5)	1·0(4)	−0·6(5)
C(8)	3·1(5)	3·3(6)	4·6(6)	−0·9(4)	0·3(4)	−0·3(5)
C(9)	3·5(4)	3·2(6)	4·6(5)	0·2(4)	0·9(4)	0·5(5)
C(10)	3·1(5)	4·4(6)	5·7(7)	0·2(5)	0·5(5)	0·5(6)
C(11)	4·6(7)	5·8(8)	11·1(13)	1·3(7)	1·9(7)	3·1(9)
C(12)	7·4(9)	4·4(8)	13·0(16)	1·7(7)	4·7(11)	0·2(9)
C(13)	6·3(8)	5·7(9)	8·7(10)	−1·1(7)	2·1(7)	−1·1(8)
C(14)	4·9(7)	6·0(8)	6·3(8)	0·4(6)	0·9(6)	−1·5(7)
C(15)	3·7(5)	3·7(6)	5·3(7)	0·3(5)	1·0(5)	−0·7(5)
C(16)	6·8(8)	6·0(9)	8·3(9)	−1·2(7)	0·0(7)	−3·5(8)
C(17)	7·2(9)	5·2(8)	12·0(15)	0·5(7)	4·1(9)	−1·5(9)
C(18)	8·4(10)	6·2(9)	7·5(9)	4·5(8)	−0·2(8)	0·3(8)

*E.s.d.'s in unit of the last significant figure.

Acknowledgements—We gratefully acknowledge support by PHS Research Grant No. GM 16924-03 from the National Institute of General Medical Sciences and by grants from the NSF (No. GB-12278), the Research Corporation and the Sloan Foundation to a consortium at the Rockefeller University for a 220 MHz NMR facility.

REFERENCES

[1]W. E. Stewart and T. H. Siddall, III, *Chem. Rev.* **70**, 517 (1970)
[2]A. Mannschreck, *Tetrahedron Letters* 1341 (1965); H. Kessler and A. Rieker, *Z. Naturforsch* **22b**, 456 (1967); *Liebigs Ann.* **708**, 57 (1967)
[3]H. Kessler, *Angew. Chem.* **82**, 237 (1970)
[4]C. C. Costain and J. M. Dowling, *J. Chem. Phys.* **32**, 158 (1960)
[5]F. Senti and D. Harker, *J. Am. Chem. Soc.* **62**, 2008 (1940); E. W. Hughes and W. J. Moore, *Ibid.* **71**, 2618 (1949); G. B. Carpenter and J. Donohue, *Ibid.* **72**, 2315 (1950)
[6]L. A. La Planche and M. T. Rogers, *Ibid.* **85**, 3728 (1963)
[7]T. H. Siddall, III and R. Garner, *Can. J. Chem.* **44**, 2387 (1966)
[8]R. Adams, *Record Chem. Prog.* (Koresge-Hooker Sci. Lib.) **10**, 91 (1949)
[9]Y. Shvo, E. C. Taylor, K. Mislow and M. Raban, *J. Am. Chem. Soc.* **89**, 4910 (1967) and refs therein
[10]L. M. Jackman, T. E. Kavanaugh and R. C. Haddon, *Org. Mag. Res.* **1**, 109 (1969)
[11]A. H. Lewin and M. Frucht, *Tetrahedron Letters* 1079 (1970)
[12]A. H. Lewin, M. Frucht and F. A. Bovey, *Tetrahedron Letters* 1083 (1970)
[13]A. similar argument has been used: C. H. Bushweller, J. W. O'Neill, M. H. Halford and F. H. Bissett, *J. Am. Chem. Soc.* **93**, 1471 (1971)
[14]P. Laszlo, *Progress in Nuclear Magnetic Resonance Spectroscopy* (Edited by J. W. Emsley, J. Feeney and L. M. Sutcliffe) Vol 3, Pergamon Press, Oxford (1967)

[15]A. H. Lewin, *Tetrahedron Letters* 3583 (1971); L. R. Isbrandt and M. T. Rogers, *Chem. Commun.* 1378 (1971)
[16]M. Frucht and A. H. Lewin, *Tetrahedron Letters* 3707 (1970)
[17]M. N. G. James and G. J. B. Williams, *Acta Cryst.* **B 29**, 1172 (1973)
[18]L. Pauling, *The Nature of the Chemical Bond* (3rd Edition) p. 260. Cornell University Press, Ithaca, N.Y. (1960)
[19]M. Frucht, unpublished results
[20]F. K. Winkler and J. D. Dunitz, *J. Mol. Biol.* **59**, 169 (1971); G. Allegra, G. Avitabile, E. Benedetti, M. R. Ciajolo, P. Corradini, P. Ganis, M. Goodman, A. Immirzi and C. Pedone, *Acta Cryst.* **A28**, Part S4, p. 513 (1972)
[21]W. R. Busing and H. A. Lery, *Acta Cryst.* **17**, 142 (1964)
[22]D. W. J. Cruickshank and D. E. Pilling, *Computing Methods on the Phase Problem in X-ray Crystal Analysis* (Edited by R. Pepinsky, J. M. Robertson and J. C. Speakman), p. 45, Pergamon Press, New York (1961)