# Crystal Structure of Isobutyramide and Comparison with its Conformation in Chloroform Solution as observed from Lanthanide-induced Nuclear Magnetic Resonance Shifts

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The crystal structure of isobutyramide has been determined by X-ray diffraction. Crystals are monoclinic, space group $P2_1/c$, with $a = 10.356(6)$, $b = 5.990(4)$, $c = 9.663(6)$ Å, $\beta = 108.10(5)°$, $Z = 4$. The structure was solved by direct methods and refined to R 7.6%. In the crystal, the C–H bond is *anti* to the C=O bond, with H–C–C=O 180°. In solution, the lanthanide-induced n.m.r. spectra show that the *anti*- and the *syn*-conformations of the amide group are both present.

THE purpose of the present paper was to compare the isobutyramide (IBA) conformation observed for the crystalline state with that found in solution.

It has been previously shown for a series of amides,[1] that in the crystal conformation, the C–H bond is *anti* with respect to the C=O bond of the amide group (a), whereas conformational-energy calculation for isolated molecules predict a *syn*-conformation with the C–H bond eclipsing the C=O bond (b). In solution the amide group may have either of the two conformations.

(a) *anti* $T_0 = 180°$ (b) *syn* $T_0 = 0°$

Torsion angles (T_0) for H–C–C–O
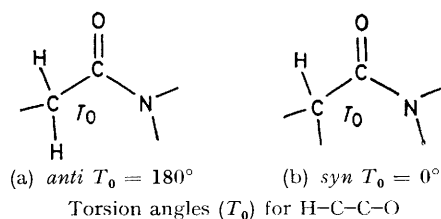
Previously,[2] we have studied the conformation in solution of 3-ethylvaleramide, EVA, and 3-propyl-hexanamide, PHA [$(C_nH_{2n+1})_2$CH·CO·NH$_2$; $n = 2$ and 3]; the n.m.r. lanthanide-induced shifts method was used.[3-6] These experiments showed that, for both compounds, the amide group has an *anti*-conformation, which is also observed for some crystalline derivatives of these amides.[7,8] Thus, these results seem to indicate that, for EVA and PHA in solution, the crystalline *anti*-conformation of the amide group should be preferred to the *syn* form predicted for the isolated molecule.

In the simple case of IBA, we wished to determine the conformation of the amide group, in both crystal and solution, and to compare these and previous results. The crystal structure was determined by X-ray diffraction.

For solution studies, the n.m.r. method, already mentioned, was used. The ^{1}H and ^{13}C resonance line induced shifts, LIS, are observed for IBA in the presence of rare-earth chelates, M(fod)$_3$ in CDCl$_3$, M = Eu, Yb, Ho, or Pr. Accordingly, the average conformation of the amide, derived from measured LIS must be considered as determined within the amide–chelate complex.

EXPERIMENTAL

Crystal Structure Determination.—Isobutyramide (Aldrich, Europe) was obtained as parallelepiped-shaped colourless single crystals by sublimation at 50 °C in a vacuum sealed glass.

Crystal data. Monoclinic, C$_4$H$_9$NO, $M = 87.12$, $a = 10.356(6)$, $b = 5.990(4)$, $c = 9.663(6)$ Å, $\beta = 108.10(5)°$, $U = 570$ Å^3, $D_m = 1.013$, $Z = 4$, $D_c = 1.015$, space group $P2_1/c$. Cu-K_α radiation, $\lambda = 1.541\ 8$ Å; μ(Cu-$K_\alpha) = 6.0$ cm^{-1}.

Three-dimensional X-ray diffraction data was collected on a four-circle diffractometer, by use of Cu-K_α radiation, by the five-point method,[9] and 614 significant diffracted intensities measured. The structure was solved by a direct multi-solution method.[10] It was refined by a full-matrix least-squares method [11] using anisotropic thermal parameters for the heavy atoms. Hydrogen atom positions were calculated or located on a Fourier difference map. For these atoms, the isotropic temperature factors (B value of the bonded carbon atom) were kept constant while the atom co-ordinates were refined. A final weighted R value of 7.6% was obtained with a weighting scheme as defined in ref. 12. The positional co-ordinates of the atoms are reported in Table 1; anisotropic thermal parameters and final observed and calculated structure factors are listed in Supplementary Publication No. SUP 22151 (14 pp.).†

Results. Figure 1 shows a projection of the molecule on the C(2), C(3), C(3') plane (ORTEP drawing [13]). Inter-

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† For details see Notice to Authors No. 7 in *J.C.S. Perkin II*, 1977, Index issue.

[1] A. T. Hagler, L. Leiserowitz, and M. Tuval, *J. Amer. Chem. Soc.*, 1976, **98**, 4600.

[2] C. Cohen-Addad and J. P. Cohen-Addad, *Spectrochim. Acta*, 1977, **33A**, 821.

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[5] A. Sievers, ' Nuclear Magnetic Resonance Shift Reagents,' Academic Press, New York, 1973.

[6] B. A. Levine and R. J. P. Williams, *Proc. Roy. Soc. (A)*, 1975, **345**, 5.

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[9] P. G. H. Troughton, Ph.D. Thesis, Chemical Crystallography Laboratory, Imperial College, London, 1969.

[10] G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, 1971, **A27**, 368.

[11] W. R. Busing and H. A. Levy, Oak Ridge National Laboratory, Report ORNL TM 271, 1962.

[12] G. H. Stout and L. H. Jensen, in ' X-Ray Structure Determination, A practical Guide,' Macmillan, London, 1968, p. 455.

[13] C. K. Johnson, Oak Ridge National Laboratory, Report. ORNL 3794, 1965.

atomic distances and bond angles are reported in Table 2, torsion angles in Table 3. The distance and angle values for the amide group are in good agreement with those generally

Atoms	x	y	z
C(1)	1 565(3)	2 287(5)	83(3)
C(2)	2 716(3)	3 842(6)	126(4)
C(3)	2 499(7)	6 092(10)	677(10)
C(3′)	4 052(5)	2 886(11)	1 020(7)
O	1 300(2)	1 788(4)	1 200(2)
N	858(3)	1 469(5)	−1 196(3)
H(2)	277(3)	404(5)	−80(3)
H(3,1)	329(5)	715(8)	77(4)
H(3,2)	165(5)	652(8)	29(5)
H(3,3)	253(5)	569(9)	159(5)
H(3′,1)	489(5)	397(8)	115(5)
H(3′,2)	407(5)	138(8)	65(5)
H(3′,3)	391(4)	253(9)	183(5)
H(N,1)	106(3)	183(5)	−201(4)
H(N,2)	21(3)	62(6)	−125(3)

* The number preceding the comma is that of the carbon atom to which each is bonded.
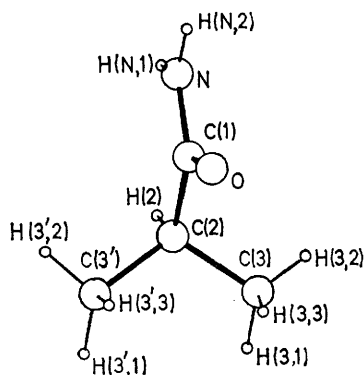

FIGURE 1 Crystalline conformation of isobutyramide: projection of the molecule in the C(2), C(3), C(3′) plane

observed. The H–C–C=O group has an *anti*-conformation (Table 4) as in many amides.[1,7,8] The methyl groups are

TABLE 2

Bond distances (Å) and bond angles (°), with estimated standard deviations in parentheses

(a) Distances

C(1)–C(2)	1.503(5)	O–C(1)	1.231(3)
C(2)–C(3)	1.492(7)	N–C(1)	1.320(4)
C(2)–C(3′)	1.498(6)		

(b) Angles

C(3)–C(2)–C(3′)	110.7(5)	N–C(1)–O	121.5(3)
C(3)–C(2)–C(1)	111.3(4)	N–C(1)–C(2)	117.4(3)
C(3′)–C(2)–C(1)	111.2(3)	O–C(1)–C(2)	121.1(3)

in a staggered conformation, and the molecules are linked through hydrogen bonds N–H · · · O of 2.89 and 2.96 Å. Table 3 also lists torsion angles for 3,4-dichloroisobutyranilide,[14] in which the isobutyramide also has an *anti*-con-

[14] G. Precigoux, B. Busetta, and M. Hospital, *Acta Cryst.*, 1976, **B32**, 943.
[15] G. Montaudo and P. Finocchiaro, *J. Org. Chem.*, 1972, **37**, 3434.

formation. The significant differences observed in the torsion-angle values may arise from variations in crystal forces.

N.m.r. Study and Conformation in Solution of Isobutyramide.—The experimental procedure was carried out as described in ref. 2.

TABLE 3

Torsion angles (°), with estimated standard deviations in parentheses, for IBA and 3,4-dichloroisobutyranilide (from ref. 14)

	IBA	3,4-Dichloro-isobutyranilide *
O–C(1)–C(2)–C(3)	−61.4(5)	−23.6
O–C(1)–C(2)–C(3′)	62.5(5)	97.7
N–C(1)–C(2)–C(3)	119.1(5)	160.3
N–C(1)–C(2)–C(3′)	−117.0(4)	−78.3
H(2)–C(2)–C(1)–O	180(3)	147
H(2)–C(2)–C(1)–N	0(3)	37

The lanthanide-induced n.m.r. shift for ¹H or ¹³C is expressed as in equation (1), where δ_0 is the pure substrate

$$\delta_{\text{obs.}} = \delta_0 + K[(3\cos^2\theta - 1)/r^3] \qquad (1)$$

chemical shift, and r and θ specify the angular co-ordinates of the ¹H or ¹³C nuclei with respect to the lanthanide. This formula only takes into account the dipolar interaction, and applies when the electronic relaxation rate of the paramagnetic centre is long and the effective symmetry of the site is considered axial.[3–6] It has been shown with Eu(fod)₃, that complex formation with amides occurs through the carbonyl group with the geometry shown in Figure 2.[15,16] An Eu–O–C–N angle of 0° is generally observed.
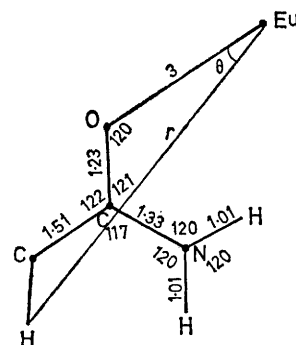

FIGURE 2 Location of europium ion in the amid group plane (ideal model; Eu–O–C–N 0°); distances (Å), angles (°)

Eu(fod)₃ (Ventron Alpha), Yb(fod)₃ and Ho(fod)₃ (Willow Brook), and Pr(fod)₃ (Spectrométrie Spin et Techniques), kept under reduced pressure with P_2O_5, were used for the determination of ¹H n.m.r. spectra. Yb(fod)₃ was only used for the ¹³C spectra because the contact interactions, usually strong for ¹³C, are in this case very weak.

Solutions of different molar ratios, $\rho = |\text{chelate}|/|\text{substrate}|$, were made by addition, in CDCl₃, of increasing weights of the chelates to a known quantity of isobutyramide. The Eu(fod)₃ spectra were observed by use of a high-resolution Cameca 250 MHz spectrometer in the continuous wave mode with tetramethylsilane as a lock and

[16] P. Finocchiaro, A. Recca, P. Maravigna, and G. Montaudo, *Tetrahedron*, 1974, **30**, 4159.

reference signal at a probe temperature of 18 °C. For the other chelates the same measurements were made with a high-resolution Varian HA-100 100 MHz spectrometer. The ¹³C spectra were observed at 30 °C with a 15 MHz Brucker spectrometer by use of the Fourier-transform technique; deuterium from $CDCl_3$ was used as a lock and tetramethylsilane as internal reference. The conditions

interpretation. As in other amides,[15] the induced shifts observed were found to be independent of the initial substrate concentration.

A single peak is associated with the methyl groups. Accordingly, these groups are geometrically equivalent, with respect to the europium atom, and have the same average conformation.

TABLE 4

Experimental induced ¹H and ¹³C shifts in isobutyramide with $Eu(fod)_3$, $Ho(fod)_3$, $Pr(fod)_3$, and $Yb(fod)_3$ in $CDCl_3$. Comparison with the calculated geometrical factor for different conformations

Atoms	δ_0/p.p.m.	Δ/p.p.m.*				$K.\delta_{calc.}$		
		$Eu(fod)_3$	$Ho(fod)_3$	$Pr(fod)_3$	$Yb(fod)_3$	(A)	(B)	$(C$
H(2)	2.42	10.27	11.3	10.60	10.75	8.6	12.3	10.1
Me	1.17	7.75	7.75	7.75	7.75	8.7	6.3	7.7
C(2)	19.7				13.0	13.0	13.0	13.0
C(3) ⎫ C(3′)⎭	35.2				8.6	9.3	7.3	8.5

* $\Delta = \Delta_{obs.} - \delta_0$ where $\Delta_{obs.}$ is the lanthanide-induced shift and δ_0 is the pure substrate chemical shift; Δ is the shift at saturation for $Eu(fod)_3$. For the other chelates the Δ values are scaled on these values, as defined in the text. $K = 1\,000$.

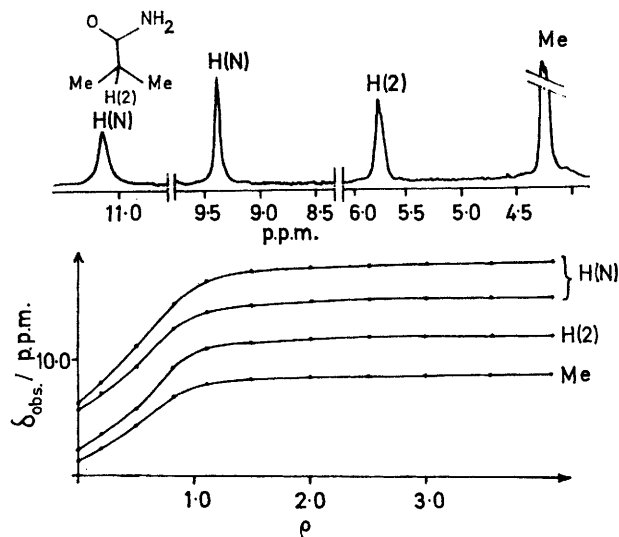in the solutions were intended to be those of complexes in fast chemical exchange.

FIGURE 3   250 MHz ¹H N.m.r. spectra in $CDCl_3$ of isobutyramide for molar ratio $\rho = |Eu(fod)_3|/substrate = 0.5$. Variation of ¹H induced shifts, $\delta_{obs.}$, with ρ; internal reference tetramethylsilane

In the present work, the stoicheiometry of the complexes was not studied. However, the fact that the different sets of proton LIS measurements were consistent, independently of the lanthanide used and also of the initial substrate concentration, insured that only one kind of species was present in the solutions.

Results.—Proton-induced shifts in IBA. (a) $Eu(fod)_3$ *spectra.* The spectra and the plot of observed induced shifts, $\delta_{obs.}$, defined in equation (1), as functions of the molar ratio, ρ, are shown in Figure 3. The shift values at saturation, $\Delta = \Delta_{obs.} - \delta_0$, are reported in Table. The estimated accuracy is *ca.* 0.02 p.p.m. The H(2) and H(N) curves are not linear. As the measurements were made up to saturation, the initial slopes of the curves were not used. Contact interactions could not be neglected for the H(N) protons which were not considered in the spectra

(b) $Yb(fod)_3$ *and other chelate spectra.* $\delta = \delta_{obs.} - \delta_0$ values of shifts induced by $Yb(fod)_3$, $Pr(fod)_3$, and $Ho(fod)_3$ as functions of ρ, with $\delta_{obs.}$ and δ_0 as already above, are reported in Figure 4. As commonly used,[4] values of ρ, up to 0.66, were investigated. In the case of $Ho(fod)_3$, a large broadening effect limited the measurements to low values of ρ. The curves were straight lines whose slopes were calculated using a regression analysis (100–2–ST3 Wang 600 computer program) and led to the Δ values reported in Table 4 with an estimated accuracy of 0.15 p.p.m. These values were not obtained at saturation but were scaled
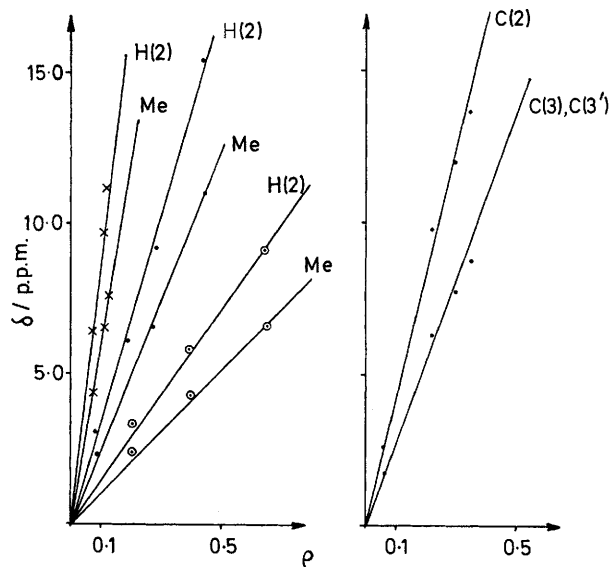

FIGURE 4   Variation of ¹H and ¹³C induced shifts, $\delta = \delta_{obs.} - \delta_0$, with molar ratio $\rho = |Ln(fod)_3|/substrate$. $\delta_{obs.}$ is the observed induced shifts at ρ ratio and δ_0, the chemical shift for pure isobutyramide in $CDCl_3$·Ln = Yb, Pr, or Ho for ¹H, and Yb only for ¹³C spectra. Full circles, spectra with $Yb(fod)_3$; crosses, spectra with $Ho(fod)_3$, and open circles with dot, spectra with $Pr(fod)_3$

against $Eu(fod)_3$ measurements, taking the methyl Δ value obtained with $Eu(fod)_3$ at saturation as a reference. The four sets were in agreement.

These results show that the average conformation of the

amide within the complexes is independent of the nature of the lanthanide used and of the ρ ratio. Thus, only one complex species should be formed and the location of the rare-earth ion with respect to the amide must be the same.

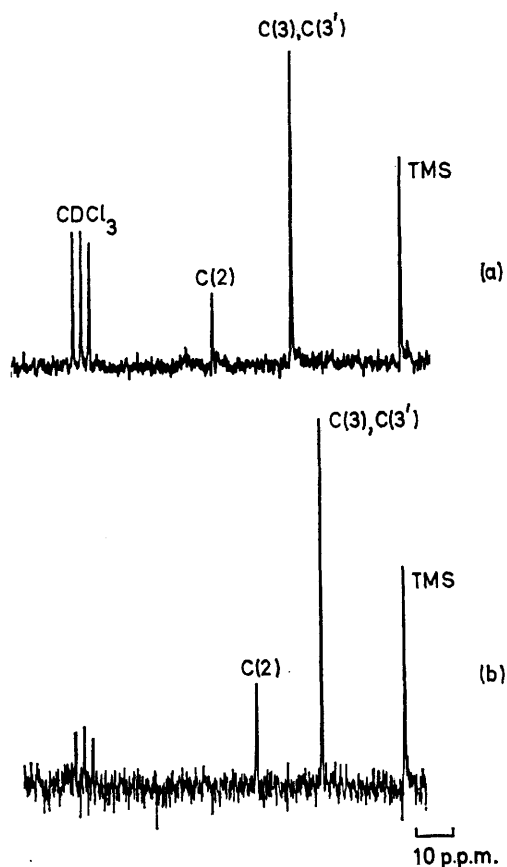*Carbon-13 induced shifts in* IBA. ^{13}C induced shifts by Yb(fod)$_3$ and spectra are shown in Figures 4 and 5. δ and

FIGURE 5 ^{13}C N.m.r. spectra of isobutyramide in CDCl$_3$; internal reference tetramethylsilane (TMS). (a) IBA with Yb(fod)$_3$ in CDCl$_3$ ($\rho = 0.225$); (b) pure IBA in CDCl$_3$

δ_0 values are reported in Table 4, with an estimated accuracy of 0.2 p.p.m. C(3) and C(3$'$) atoms, which give rise to only one resonance line, are geometrically equivalent with respect to the lanthanide ion. This result is in agreement with those obtained for ^{1}H n.m.r. spectra.

DISCUSSION

Interpretation of the N.m.r. Spectra.—The experimental results were analysed as follows, according to a

procedure used previously.[2] (i) The lanthanide ions are assumed to be located in the position represented in Figure 2. (ii) From energy calculations on amides,[1] the amide group may have two conformations in solution; in (A), the C–H is *anti* with respect to the C=O bond, as in the crystal structure, and in (B) it eclipses the carbonyl bond. For IBA, these two conformations lead to different values of the geometrical factor. $\delta_{\text{calc.}} = (3 \cos^2\theta - 1)/r^3$ which can be calculated in each case. (iii) The $\delta_{\text{calc.}}$ values were obtained by use of the crystal structure parameters. The same atomic co-ordinates were used for the *syn*-conformation with a 180° rotation of the europium amide group. The results are summarized in Table 4 and show that neither the (A) nor the (B) conformation agrees with the LIS experimental values for both ^{1}H and ^{13}C measurements.

A weighted conformation was introduced as follows: $\delta_{\text{calc.}} = p\delta_{\text{calc.}}(A) + (1-p)\delta_{\text{calc.}}(B)$. A p value of 0.60 ± 5 led to a good agreement between the observed and calculated LIS values. The comparison of $\delta_{\text{calc.}}$ with Δ saturation values obtained with Eu(fod)$_3$ (Table 4) gave a pseudo-contact constant of $1\,000 \pm 100$ p.p.m. Å^3, in good agreement with previous determinations for amides.[2,15,16]

This study has shown that in solution within the chelate–amide complex, IBA is present in two conformations: the *anti* conformation which is observed in the IBA crystal structure is the most probable, but the *syn* conformation is also present with 40% probability. However, two other amides, EVA and PHA, were found to exist only in *anti*-conformations within the same amide–chelate complex.[2]

anti-Conformations of amides are generally observed in the crystalline state while *syn*-conformations are predicted as preferential by conformational-energy calculations for the isolated molecule.[1] From present work, solutions would represent an intermediate between these two states with the possibility of coexistence of the two conformations.