

Correlation of Molecular Properties and Absolute Configuration of a Chiral Tertiary Alcohol. Crystal Structure of (+)-1-(1-Isoquinolinyl)-1-(2-pyridyl)ethyl (1-Phenylethyl)carbamate

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Csóreg, I., Elman, B. and Moberg, C., 1988. Correlation of Molecular Properties and Absolute Configuration of a Chiral Tertiary Alcohol. Crystal Structure of (+)-1-(1-Isoquinolinyl)-1-(2-pyridyl)ethyl (1-Phenylethyl)carbamate. - Acta Chem. Scand., Ser. B 42: 339-344.

The molecular and crystal structure of (+)-1-(1-isoquinolinyl)-1-(2-pyridyl)ethyl (1-phenylethyl)carbamate, derived from (-)-1-(1-isoquinolinyl)-1-(2-pyridyl)ethanol and (S)-1-phenylethyl isocyanate, has been determined from single-crystal X-ray data. The unit cell is orthorhombic ($P2_12_12_1$) with $a = 9.5879(4)$, $b = 11.9100(5)$, $c = 18.8733(11)$ Å and $Z = 4$. The structural model has been refined against 1461 reflections ($F/\sigma(F) > 6$) to $R = 0.054$. The X-ray study of the present diastereomeric carbamate has proved the relative configuration of the two chiral centres to be (*R*, *S*), as previously assigned on the basis of molecular properties, thereby extending existing empirical rules for configurational determinations to tertiary alcohols.

Assignment of the absolute configuration is a crucial part of the structure determination of chiral organic compounds. Useful empirical methods based on molecular properties have lately been developed for various kinds of molecules.¹⁻³ Thus, the absolute configurations of a large number of chiral secondary alcohols have successfully been assigned by transforming them into diastereomeric carbamates and applying arguments based on ¹H NMR spectral data and liquid chromatography elution order.⁴ We have recently used similar arguments for the assignment of the absolute configuration of a pair of enantiomeric tertiary alcohols.⁵ Since the development of methods for the determination of the absolute configurations of new kinds of molecules is desirable, an unambiguous assignment of the absolute

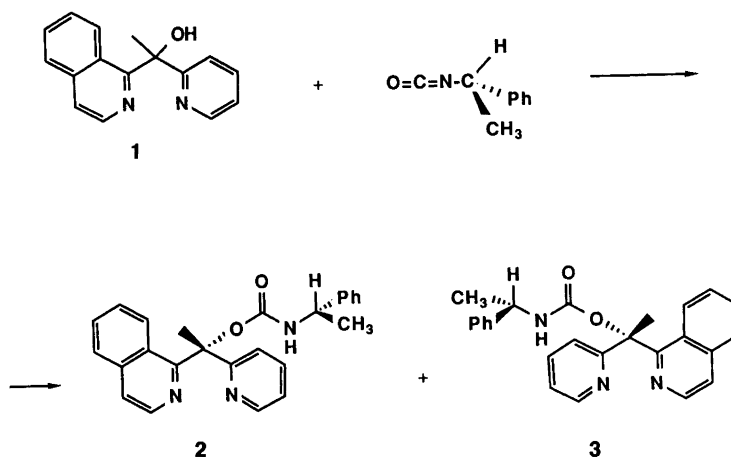
configuration of the alcohols was of interest. Therefore, an X-ray crystallographic determination of the structure of a carbamate derived from a chiral isocyanate and one of these alcohols is now presented.

Experimental

The diastereomeric carbamates **2** and **3** were obtained by reaction of (S)-1-phenylethyl isocyanate with the racemic alcohol **1** (Scheme 1). The two carbamates, with opposite signs of optical rotation, were separated by liquid chromatography on a silica gel column using EtOAc:petroleum ether (7:3). The (+)-carbamate, which was eluted last, was crystallized from ethyl acetate. The crystals, with the empirical formula $C_{25}H_{23}N_3O_2$ ($M_w = 397.5$, $D_c = 1.225$ g cm⁻³), show the orthorhombic space group symmetry $P2_12_12_1$. The unit cell has $a = 9.5879(4)$, $b = 11.9100(5)$ and $c = 18.8733(11)$ Å, with $Z = 4$. The X-ray data were measured at room temper-

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Scheme 1.

ature using a Siemens/STOE AED2 computer-controlled diffractometer, graphite-monochromated $\text{CuK}\alpha$ radiation ($\lambda = 1.5418 \text{ \AA}$) and $\omega-2\theta$ scan technique. The intensities of 2257 reflections ($\theta_{\text{max}} = 70^\circ$) were collected for a colourless single crystal with the approximate dimensions $0.18 \times 0.52 \times 0.44 \text{ mm}$. The net intensities were corrected for Lorentz and polarization effects, but the rather small absorption effects ($\mu = 5.5 \text{ cm}^{-1}$) were neglected. The unit cell dimensions were refined using the angular settings of 39 well-centered reflections ($38^\circ < 2\theta < 58^\circ$), accurately measured on the diffractometer. An initial structural model, comprising all the non-hydrogen atoms of the molecule, was obtained with the MULTAN program system.⁶ This model was then

extended and refined with the programs of the SHELX system.⁷ In the last cycles of the refinement the non-hydrogen atoms were allowed to vibrate anisotropically, while the hydrogen positions, derived from difference electron density calculations, were refined together with their isotropic temperature factors. Thus, the full-matrix least-squares calculation converged to a final linear R value of 0.054 for 1461 reflections, all with $F/\sigma(F) > 6$. The weighted $R = [\sum w|\Delta F|^2 / \sum w|F_o|^2]^{1/2}$ became 0.070. The weights of the observed structure factors were calculated as $w = 1.0/[\sigma^2(F_o) + 0.01847 F_o^2]$, with $\sigma(F_o)$ derived from counting statistics.

Lists of coordinates and isotropic temperature factors of the hydrogen atoms, bond lengths and

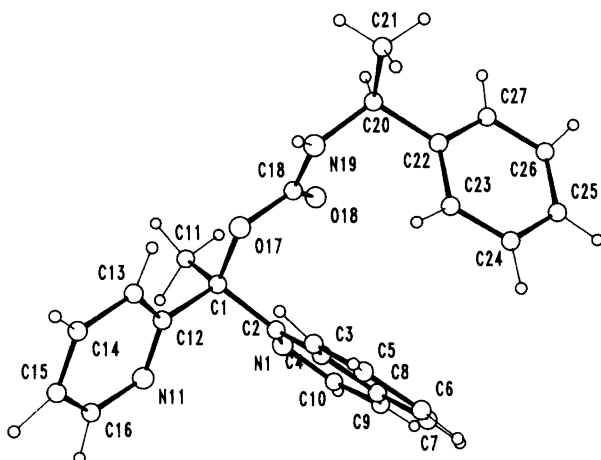


Fig. 1. Perspective view of the molecule, showing also the numbering of the atoms.

Table 1. Fractional atomic coordinates and equivalent isotropic temperature factors with e.s.d.'s for the non-hydrogen atoms.

Atom	<i>x/a</i>	<i>y/b</i>	<i>z/c</i>	$U_{eq} / \text{\AA}^2$
C(1)	0.5990(5)	-0.0141(4)	0.2767(3)	0.055(2)
N(1)	0.6577(5)	-0.1708(3)	0.2016(2)	0.061(2)
C(2)	0.6418(5)	-0.0614(4)	0.2049(3)	0.054(2)
C(3)	0.6645(5)	0.0111(4)	0.1441(3)	0.056(2)
C(4)	0.6595(6)	0.1299(4)	0.1472(3)	0.065(2)
C(5)	0.6822(7)	0.1897(5)	0.0862(4)	0.076(2)
C(6)	0.7097(8)	0.1391(5)	0.0217(4)	0.081(2)
C(7)	0.7150(7)	0.0238(5)	0.0167(4)	0.073(2)
C(8)	0.6938(5)	-0.0413(4)	0.0786(3)	0.058(2)
C(9)	0.7052(7)	-0.1603(5)	0.0771(3)	0.064(2)
C(10)	0.6898(7)	-0.2190(4)	0.1377(3)	0.071(2)
C(11)	0.5613(7)	-0.1057(4)	0.3299(3)	0.066(2)
N(11)	0.8368(5)	0.0057(4)	0.3132(3)	0.071(2)
C(12)	0.7147(5)	0.0582(4)	0.3097(3)	0.058(2)
C(13)	0.6925(7)	0.1663(4)	0.3339(3)	0.070(2)
C(14)	0.8038(7)	0.2208(5)	0.3661(4)	0.082(2)
C(15)	0.9296(8)	0.1676(6)	0.3710(4)	0.091(3)
C(16)	0.9411(7)	0.0610(7)	0.3448(4)	0.084(3)
O(17)	0.4814(3)	0.0627(3)	0.2675(2)	0.057(1)
C(18)	0.3665(5)	0.0254(4)	0.2323(3)	0.062(2)
O(18)	0.3469(4)	-0.0710(3)	0.2161(3)	0.077(2)
N(19)	0.2799(5)	0.1122(3)	0.2198(3)	0.062(2)
C(20)	0.1506(6)	0.0947(4)	0.1795(3)	0.064(2)
C(21)	0.0666(7)	0.2024(6)	0.1814(5)	0.081(3)
C(22)	0.1780(6)	0.0570(4)	0.1035(3)	0.061(2)
C(23)	0.2981(6)	0.0859(5)	0.0675(3)	0.072(2)
C(24)	0.3183(7)	0.0530(7)	-0.0023(4)	0.085(3)
C(25)	0.2178(9)	-0.0083(6)	-0.0364(4)	0.088(2)
C(26)	0.0997(9)	-0.0377(5)	-0.0016(4)	0.090(3)
C(27)	0.0783(7)	-0.0047(5)	0.0683(4)	0.078(2)

$$^a U_{eq} = \frac{1}{3} \sum_j \sum_j U_{ij} \cdot \mathbf{a}_i^* \cdot \mathbf{a}_j^* \cdot \mathbf{a}_i \cdot \mathbf{a}_j$$

Table 2. Intramolecular bond distances between the non-hydrogen atoms, with e.s.d.'s in parentheses.

Atoms	Distance/\AA	Atoms	Distance/\AA
C(1) – C(2)	1.524(7)	C(1) – C(11)	1.526(7)
C(1) – C(12)	1.537(7)	C(1) – O(17)	1.462(5)
N(1) – C(2)	1.314(6)	N(1) – C(10)	1.371(5)
C(2) – C(3)	1.452(7)	C(3) – C(4)	1.417(7)
C(3) – C(8)	1.414(7)	C(4) – C(5)	1.371(9)
C(5) – C(6)	1.384(9)	C(6) – C(7)	1.377(9)
C(7) – C(8)	1.416(8)	C(8) – C(9)	1.421(7)
C(9) – C(10)	1.349(8)	N(11) – C(12)	1.329(7)
N(11) – C(16)	1.338(8)	C(12) – C(13)	1.382(7)
C(13) – C(14)	1.389(9)	C(14) – C(15)	1.365(10)
C(15) – C(16)	1.367(10)	O(17) – C(18)	1.362(6)
C(18) – O(18)	1.203(6)	C(18) – N(19)	1.347(6)
N(19) – C(20)	1.468(7)	C(20) – C(21)	1.515(9)
C(20) – C(22)	1.526(8)	C(22) – C(23)	1.381(8)
C(22) – C(27)	1.377(8)	C(23) – C(24)	1.388(9)
C(24) – C(25)	1.370(10)	C(25) – C(26)	1.355(10)
C(26) – C(27)	1.391(10)		

bond angles involving the hydrogens, equations of the LS planes, deviations of selected atoms from the planes, dihedral angles between the calculated planes, anisotropic thermal parameters of the non-hydrogen atoms, and a list of the observed and calculated structure factors have been deposited with the British Library Lending Division. Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England, and also from the authors.

Results and discussion

The numbering of the atoms of the (+)-carbamate is shown in Fig. 1. The molecule has two asymmetric carbon atoms. The absolute configuration of the chiral centre at C(1) proved to be *R*. This could be deduced directly from the molecular geometry, since the chiral C(20) atom was known to have *S* configuration⁵ (cf. Fig. 1). The atomic coordinates, listed in Table 1, refer to the correct diastereomer. The bond distances and angles, listed in Tables 2 and 3, generally conform to the expected values. Four parts of the molecule were examined for planarity: the isoquinoline (plane 1), the pyridine (plane 2) and the phenyl (plane 3) rings, and the carbamate group (plane 4). The dihedral angle between the planes through the two fused rings of the isoquinoline moiety is 2.9(2)°, and the ten ring atoms deviate less than 0.05 Å from the calculated plane 1. The ring atoms of the pyridine and the phenyl rings are coplanar to within 0.021 and 0.008 Å, respectively. The atoms O(17)–C(18)–O(18)–N(19)–C(20), forming the carbamate group, are also coplanar to within 0.048 Å. The dihedral angle between this latter plane and the plane through the pyridine ring is 17.1(2)°. As can be seen in Fig. 1, the pyridine ring and the C(21) methyl carbon lie approximately in the carbamate plane. The torsional angles calculated for C(12)–C(1)–O(17)–C(18) and C(18)–N(19)–C(20)–C(21) are 173.4(4)° and 173.3(5)°, respectively. The two bulky substituents, i.e. the isoquinolinyl and phenyl groups, are located on one side of the carbamate plane, while the C(11) methyl group is on the other. In the crystal structure there is an intermolecular hydrogen bond from the amine hydrogen atom to the isoquinoline N atom [N(19)⋯N(1)[$-x+1, y+\frac{1}{2}, -z+\frac{1}{2}$] = 3.040(5), N(19)–H(19) = 0.99(6), H(19)⋯N(1) = 2.13(6)

Table 3. Intramolecular bond angles (with e.s.d.'s) involving the non-hydrogen atoms.

Atoms involved	Angle/°
C(12)–C(1)–O(17)	104.7(4)
C(11)–C(1)–O(17)	110.1(4)
C(11)–C(1)–C(12)	107.7(4)
C(2)–C(1)–O(17)	109.5(4)
C(2)–C(1)–C(12)	111.9(4)
C(2)–C(1)–C(11)	112.7(4)
C(2)–N(1)–C(10)	118.8(4)
C(1)–C(2)–N(1)	116.0(4)
N(1)–C(2)–C(3)	122.4(4)
C(1)–C(2)–C(3)	121.6(4)
C(2)–C(3)–C(8)	117.3(4)
C(2)–C(3)–C(4)	123.8(5)
C(4)–C(3)–C(8)	118.9(5)
C(3)–C(4)–C(5)	118.6(5)
C(4)–C(5)–C(6)	122.8(6)
C(5)–C(6)–C(7)	120.1(6)
C(6)–C(7)–C(8)	119.0(6)
C(3)–C(8)–C(7)	120.5(5)
C(7)–C(8)–C(9)	121.3(5)
C(3)–C(8)–C(9)	118.2(5)
C(8)–C(9)–C(10)	119.4(5)
N(1)–C(10)–C(9)	123.6(5)
C(12)–N(11)–C(16)	116.6(5)
C(1)–C(12)–N(11)	113.1(4)
N(11)–C(12)–C(13)	123.9(5)
C(1)–C(12)–C(13)	123.0(5)
C(12)–C(13)–C(14)	117.5(5)
C(13)–C(14)–C(15)	119.4(6)
C(14)–C(15)–C(16)	118.6(7)
N(11)–C(16)–C(15)	123.9(6)
C(1)–O(17)–C(18)	118.5(3)
O(17)–C(18)–N(19)	109.5(4)
O(17)–C(18)–O(18)	124.2(5)
O(18)–C(18)–N(19)	126.3(5)
C(18)–N(19)–C(20)	120.2(4)
N(19)–C(20)–C(22)	112.5(4)
N(19)–C(20)–C(21)	108.5(5)
C(21)–C(20)–C(22)	111.3(5)
C(20)–C(22)–C(27)	119.5(5)
C(20)–C(22)–C(23)	122.2(5)
C(23)–C(22)–C(23)	122.2(5)
C(23)–C(22)–C(27)	118.3(5)
C(22)–C(23)–C(24)	120.9(6)
C(23)–C(24)–C(25)	119.9(6)
C(24)–C(25)–C(26)	119.8(7)
C(25)–C(26)–C(27)	120.7(7)
C(22)–C(27)–C(26)	120.4(6)

Å and $\angle N(19)–H(19)⋯N(1) = 152(5)^\circ$] (Fig. 2). This bond links the molecules so as to form infinite chains in the direction of the *b* axis. The

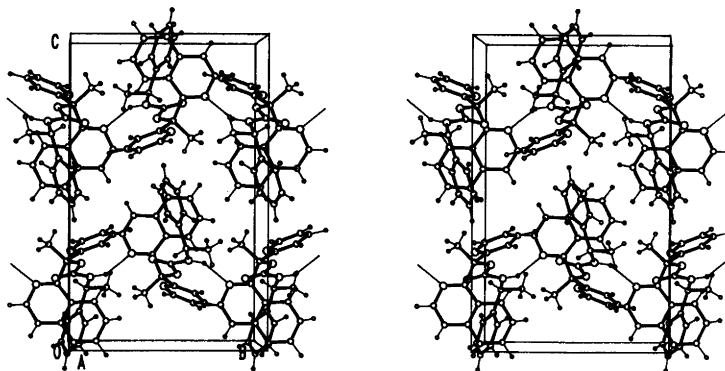


Fig. 2. Stereoscopic packing diagram of the crystal structure.

hydrogen bond leads to two relatively short intermolecular contacts, viz. $O(18)\cdots C(14) = 3.262(7)$ and $O(18)\cdots C(13) = 3.290(6)$ Å, but all the other intermolecular contacts have normal van der Waals interaction lengths.

The success of chromatographic separations and configurational assignments of carbamates derived from secondary alcohols is a consequence of the planarity and rigidity of the $HCOC(O)N(H)CH$ system (Fig. 3). The diastereomer containing the two sterically least bulky groups on the same side of the carbamate plane has the strongest interaction with the stationary phase, and is thus eluted last.

Also in the present carbamate, derived from a tertiary alcohol, the $OC(O)NC$ atoms are situated in one plane, and it may be assumed that in solution its amine part adopts a conformation similar to that in carbamates derived from secondary alcohols. The interaction with the stationary phase will thus depend on the conformation of the alcohol part of the molecule. Our previous assignment⁵ of the relative configurations of the two chiral centres was based on the relative elution order of the diastereomeric carbamates and on 1H NMR spectral data, which both suggest that the pyridine ring in the (+)-carbamate is

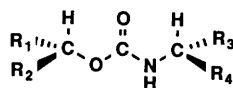


Fig. 3. Conformation of a carbamate derived from a secondary alcohol.

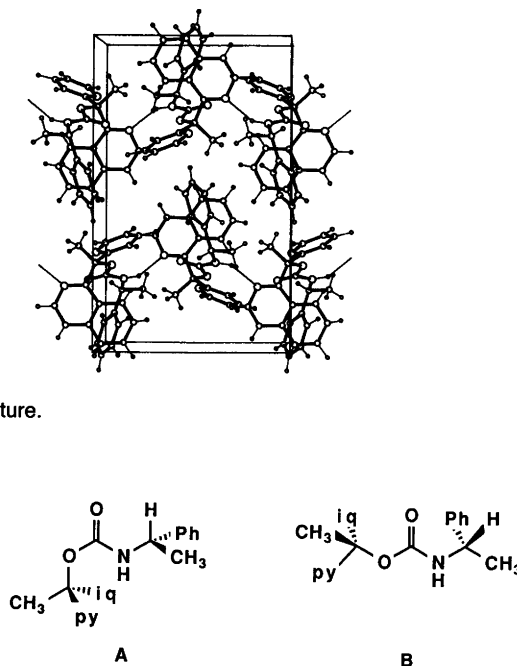


Fig. 4. Possible conformations of carbamate 2; iq = isoquinoline, py = pyridine.

situated *syn* to the methyl group in the amine part of the molecule, and IR data which suggest that there is a hydrogen bond from the amine hydrogen to the pyridine or isoquinoline nitrogen atoms (A, Fig. 4). This crystallographic study shows, however, that the molecule in the crystalline state adopts a different conformation, which may be represented by B in Fig. 4. However, in both conformations, one face of the molecule exposes the two bulkiest substituents, i.e. the phenyl and the isoquinoline groups. It is thus expected that the isomer having the stronger interaction with the stationary phase should have the (*R,S*) configuration, in accordance with the present findings.

Acknowledgements. We thank Professor Peder Kierkegaard, University of Stockholm, for his stimulating interest and encouragement in this project. This work was supported by the Swedish Natural Science Research Council and by the Swedish Board for Technical Development.

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Received October 28, 1987.