Derivatives of Optically Active 1-Chloro-2,2-bismethoxycarbonylaziridine: Absolute Configuration and X-Ray Molecular Structure of (−)-(*E*)-1-Chloro-2-methoxycarbonyl-2-methylcarbamoylaziridine

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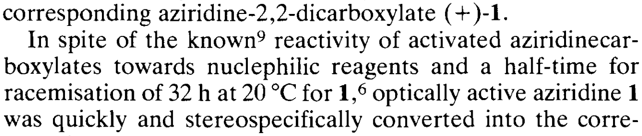
X-Ray analysis of (−)-(*E*)-1-chloro-2-methoxycarbonyl-2-methylcarbamoylaziridine shows that the absolute configuration at the chiral centres is (−)-(1*R*,2*R*); this enables us to assign the *S* configuration to the chiral nitrogen atom in the related compound (+)-1-chloro-2,2-bismethoxycarbonylaziridine.

There has been growing interest in optically active aziridines as chiral synthons in organic synthesis[1] in recent years. In particular, aziridine-2-carboxylates have a potential role in the synthesis of amino acids.[2,3] The chemistry of aziridines in general and the intrinsic high reactivity of their three-membered ring have been reported.[4] However, relatively little has been written regarding the synthesis of aziridinecarboxylates[5–7] in an optically active form and of known absolute configuration, and even less about aziridines whose chirality is due solely to the trivalent nitrogen atom.[8]

Recently, we found[6] that hydrolases differentiate very effectively between the enantiomers of three-membered heterocycles containing a chiral nitrogen atom and ester groups on the ring carbon atom. The enantioselective enzymatic hydrolysis of racemic 1-chloro-2,2-bismethoxycarbonylaziridine **1**, catalysed by α-chymotrypsin or lipase from *Rhizopus delemar* thus afforded **1** in good chemical (40%) and optical yields [50–70% enantiomeric excess (e.e.)].[6]

We now report the synthesis, X-ray structure and absolute configuration of the optically pure (−)-(*E*)-1-chloro-2-methoxycarbonyl-2-methylcarbamoylaziridine **2** obtained by amidation of (+)-**1** and epimerisation of the invertomer (+)-(*Z*)-**2**. This enabled us to correlate the configuration at the chiral nitrogen atom of (−)-(*E*)-**2** with that of the corresponding aziridine-2,2-dicarboxylate (+)-**1**.

In spite of the known[9] reactivity of activated aziridinecarboxylates towards nuclephilic reagents and a half-time for racemisation of 32 h at 20 °C for **1**,[6] optically active aziridine **1** was quickly and stereospecifically converted into the corresponding 1-chloro-2,2-dicarboxyaziridine monomethylester monomethylamide **2** simply by treatment with methylamine at −5 °C. When a dichloromethane solution of crude (+)-**1** (50% e.e.), obtained by an α-chymotrypsin-catalysed resolution, was treated with an excess of methylamine at −5 °C (20 min), the corresponding monoamide **2** {$[\alpha]_D^{20}$ +59.5° (*c* 1.5, $CHCl_3$)} was afforded in nearly quantitative yield (80%) and in a single diastereoisomeric form (as indicated by ^{1}H NMR spectroscopy). This derivative was shown to correspond to the



(+)-(*S*)-**1** (+)-(1*S*,2*R*)-(*Z*)-**2** (−)-(1*R*,2*R*)-(*E*)-**2**

Scheme 1

Z-isomer from the X-ray analysis of E-epimer. The crystallisation of (+)-(Z)-**2** from diethyl ether at −30 °C allowed the separation of a liquid enantiomerically enriched sample {50% yield; $[\alpha]_D^{20}$ +103.9° (c 0.6, $CHCl_3$)} from the solid racemate. Its ^1H NMR spectrum, recorded in the presence of the chiral solvating agent (R)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol, suggested that its enantiomeric purity was not less than 90%.

A solution of (+)-(Z)-**2** in tetrachloromethane, heated at 50 °C, for 5 h revealed the presence in the ^1H NMR spectrum of both the invertomers at the aziridine ring nitrogen atom in a 4:1 ratio (Z:E). A 'second-order asymmetric transformation'[10] was involved in this epimerisation. The (−)-(E)-**2** invertomer thus formed was solid and slightly soluble in CCl_4, which can be continuously removed from the solution by precipitation. The crystallisation from dichloromethane–n-hexane afforded the diastereoisomerically- and enantiomerically-pure isomer, (−)-(E)-**2**{$[\alpha]_D^{20}$ −91.8 (c 0.5, $CHCl_3$)}. X-Ray diffraction analysis has shown that the absolute configuration at the chiral N(1) and C(2) centres is (−)-(1R,2R), (Fig. 1).

The crystal structure,† built up of one crystallographically independent molecule, was solved using direct methods and refined through full-matrix least-squares calculations to a final R factor of 0.027. The absolute configuration was determined through refinement of Roger's η parameter, whose final value was 1.01(14).

The bond distances and bond angles of compound (E)-**2** are in the expected range.[8,11] The methoxycarbonyl and methylcarbamoyl groups, planar within ±0.033 Å, are at dihedral angles of 80.5° and 59.6°, respectively, to the aziridine ring plane, and of 70.8° to each other. The crystal packing is mainly determined by one strong intermolecular N–H · · · O hydrogen-bonding interaction involving the amidic function, which ties the molecules onto linear chains paralleling the a-cell axis. These chains interact through some short van der Waals contacts (from 3.016 to 3.597 Å), involving mainly carboxylate oxygens.

X-ray diffraction analysis of (−)-(1R,2R)-(E)-**2** affords an unambiguous picture of the stereochemical course of the transformation of (+)-**1** into (−)-(E)-**2** (Scheme 1). Since amidation of **1** does not involve the nitrogen chiral centre, compounds **1** and (Z)-**2** must have the same configuration at the nitrogen atom that is opposite in (E)-**2**. Thus, we can assign the (S) configuration to the chiral nitrogen atom in (+)-**1** and (1S,2R) configuration to the (+)-(Z)-**2** compound.

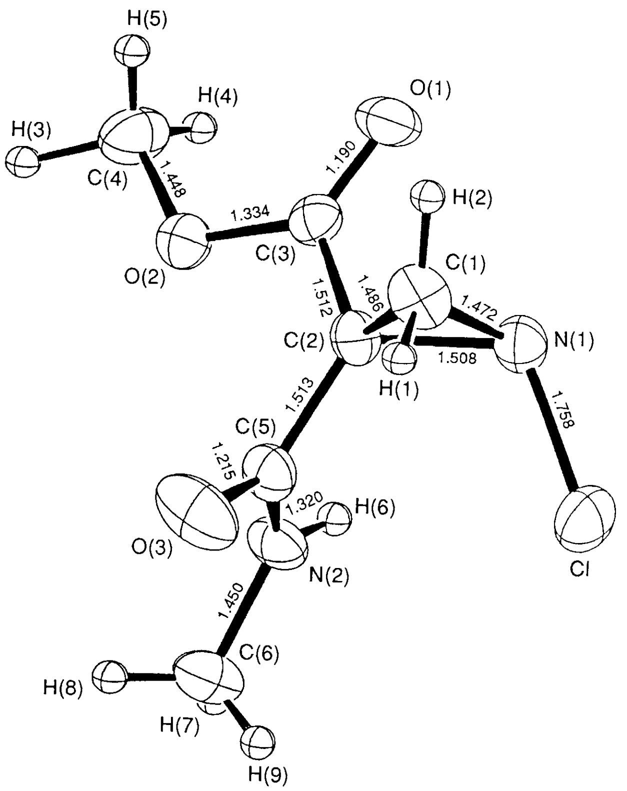


Fig. 1 ORTEP view of the molecule showing the atom numbering, thermal motion ellipsoids (40%) for non-H atoms and bond distances (Å). The range of their esds is ± 0.002–0.003 Å.

The authors thank the Ministry of Education for financial support.

Received, 3rd December 1990; Com. 0/05433J

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† *Crystal data* for: $C_6H_9ClN_2O_3$, M = 192.602, orthorhombic, a = 4.722(1), b = 10.847(1), c = 17.104(2) Å, U = 876.1 Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.460 g cm^{-3}, colourless, air-stable prisms. Crystal dimensions 0.34 × 0.28 × 0.28 mm, μ(Mo-Kα) = 3.5 cm^{-1}. Intensity data were collected at room temperature with graphite-monochromated Mo-Kα radiation (λ = 0.71069 Å) on a CAD4 diffractometer. Of 2332 measured reflections (θ 1.5–27 °), 1846 had $I > 3\sigma(I)$, and 1560, including Bijvoet pairs, were independent (R_m = 1.12%), and were used (without absorption correction) in the structure analysis. The structure was solved by direct methods and refined through full-matrix least-squares calculations, anistropically for non-hydrogen atoms and isotropically for hydrogen atoms, to final R = 2.72% and R_w = 3.07%. The absolute configuration was determined through refinement of Roger's η parameter, whose final value was 1.01 (14). Also Hamilton's R-factor test, after refinement of the inverted model (R = 2.87% and R_w = 3.26%), confirmed the reliability of our assignment of 0.005 significance level. SHELXTL software (5.1) G. Sheldrick, Nicolet XRD, Madison, WI (USA). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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