References

Altomare, A., Cascarano, G., Giacovazzo, C. & Guagliardi, A. (1993). *J. Appl. Cryst.* **26**, 343–350.

Enraf–Nonius (1992). *CAD-4-PC Software*. Version 1.1. Enraf–Nonius, Delft, The Netherlands.

Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

Molecular Structure Corporation (1992). *TEXSAN. TEXRAY Structure Analysis Package*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

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Absolute Configuration of (+)-α-Methyl-4-carboxyphenylglycine (MCPG), a Metabotropic Glutamate Receptor Antagonist

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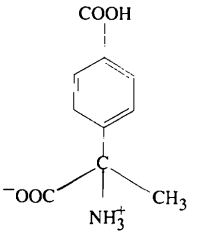
Abstract

The title compound, (+)-MCPG [(+)-α-(4-carboxyphenyl)-α-methylglycine, $C_{10}H_{11}NO_4$], is an antagonist at certain subtypes of metabotropic glutamate (mGlu) receptors. (+)-MCPG has gained widespread acceptance as a tool for probing the physiological role of mGlu receptors in the central nervous system. As a result, mGlu receptors are now known to be involved in processes connected with learning and memory, modulation of synaptic transmission and the transmission of pain responses. (+)-MCPG crystallized in its zwitterionic form. Its absolute configuration was assigned as *S* from X-ray diffraction data collected at 150 K. The refined Flack parameter is consistent with this assignment, although the large e.s.d. associated with it introduces some ambiguity.

Comment

To date, molecular biologists have cloned eight subtypes of metabotropic glutamate (mGlu) receptors, termed $MGlu_{1-8}$ (Pin & Duvoisin, 1995). Although a number of selective agonists have been identified for these receptors, no competitive antagonists were known at the outset of this project. We introduced (+)-α-methyl-4-carboxyphenylglycine [(+)-MCPG] as an antagonist of mGlu receptors present in the neonatal rat spinal cord (Jane *et al.*, 1993; Kemp *et al.*, 1994) and subsequently reported antagonist actions of MCPG on cloned mGlu receptors expressed in Chinese hamster ovary cells (Hayashi *et al.*, 1994). As a result of this work, (+)-MCPG has gained widespread use as a tool for probing the physiological roles of mGlu receptors in the central nervous system (Watkins & Collingridge, 1994; Knöpfel, Kuhn & Allgeier, 1995). The determination of the absolute configuration of (+)-MCPG is therefore an important aid in the design of more potent and selective mGlu receptor antagonists.



(+)-MCPG

(+)-MCPG crystallizes in its zwitterionic form, with the C1, O1 and O2 atoms forming the COO^- group. The two C—O bond lengths are not identical, but differ by 0.021 (4) Å. This may be due to the greater involvement of the O1 atom in hydrogen bonds compared with O2. A similar difference (0.016 Å) was noted in the neutron structure of L-alanine (Lehmann, Koetzle & Hamilton, 1972). The three H atoms of the NH_3^+ group were located in difference Fourier maps and, as for the other H atoms, positional and U_{iso} parameters were refined. All three H atoms are involved in a hydrogen-bonding network, details of the geometry of which are given in Table 2 and Fig. 2.

The Flack absolute structure parameter (Flack, 1983) was refined; expected values are 0 for the correct and +1 for the inverted absolute structure. The refined value

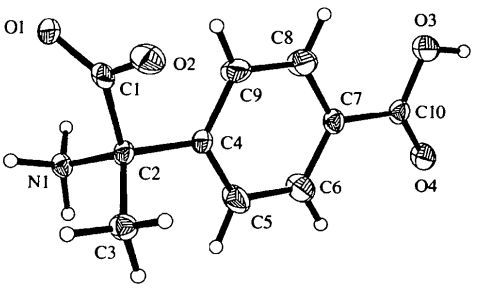


Fig. 1. View showing the labelling of the non-H atoms of (+)-MCPG. Displacement ellipsoids are drawn at the 50% probability level and H atoms are drawn as small circles of arbitrary radii.

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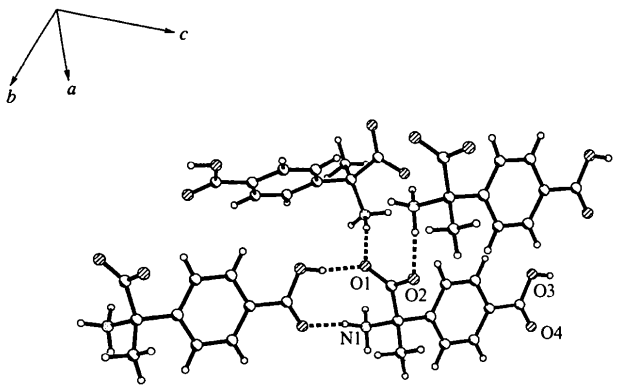

Fig. 2. View showing hydrogen-bonding interactions (indicated by dashed lines) in (+)-MCPG. Symmetry equivalents (i), (ii) and (iii) are drawn (i)–(iii) in a clockwise direction from the bottom left (labels are as given in Table 2).

of −0.15 (28) is consistent with the assignment of the configuration of (+)-MCPG as *S*, although the large e.s.d. means that this assignment is not unambiguous.

Experimental

Racemic MCPG was synthesized and resolved to give the individual enantiomers by the method reported by Hayashi *et al.* (1994).

Crystal data

$C_{10}H_{11}NO_4$
M_r = 209.20
Monoclinic
$P2_1$
a = 8.698 (3) Å
b = 5.819 (3) Å
c = 10.032 (3) Å
β = 107.48 (3)°
V = 484.3 (3) Å^3
Z = 2
D_x = 1.435 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 25 reflections
θ = 30–38°
μ = 0.948 mm^{-1}
T = 150 (2) K
Rectangular
0.3 × 0.2 × 0.2 mm
Colourless

Data collection

Rigaku AFC-6*S* four-circle diffractometer
θ–2θ scans
Absorption correction: none
2279 measured reflections
2205 independent reflections
1952 reflections with $I > 3\sigma(I)$

R_{int} = 0.0192
θ_{max} = 75.01°
$h = -10 \rightarrow 0$; $0 \rightarrow 10$
$k = -7 \rightarrow 0$; $0 \rightarrow 7$
$l = -12 \rightarrow 12$; $-12 \rightarrow 12$
3 standard reflections
every 150 reflections
intensity decay: 0.3%

Refinement

Refinement on F^2
$R(F)$ = 0.0346
$wR(F^2)$ = 0.0881
S = 1.001
1816 reflections
180 parameters

$\Delta\rho_{max}$ = 0.230 e Å^{-3}
$\Delta\rho_{min}$ = −0.173 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

All H atoms refined
$w = 1/[\sigma^2(F_o^2) + (0.0376P)^2 + 0.3572P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = −0.007

Absolute configuration: Flack (1983)
Flack parameter = −0.15 (28)

Table 1. *Selected geometric parameters (Å, °)*

O1—C1	1.267 (3)	C4—C5	1.380 (4)
O2—C1	1.247 (3)	C4—C9	1.390 (4)
O3—C10	1.322 (3)	C5—C6	1.396 (3)
O4—C10	1.213 (3)	C6—C7	1.386 (4)
N1—C2	1.500 (3)	C7—C8	1.378 (4)
C1—C2	1.540 (3)	C7—C10	1.495 (3)
C2—C3	1.530 (3)	C8—C9	1.384 (3)
C2—C4	1.539 (3)		
O2—C1—O1	126.1 (2)	N1—C2—C1	108.4 (2)
O2—C1—C2	116.0 (2)	C3—C2—C1	109.7 (2)
O1—C1—C2	117.9 (2)	C4—C2—C1	108.9 (2)
N1—C2—C3	107.3 (2)	O4—C10—O3	123.7 (2)
N1—C2—C4	109.5 (2)	O4—C10—C7	123.7 (2)
C3—C2—C4	112.8 (2)	O3—C10—C7	112.5 (2)
O1—C1—C2—C3	−129.4 (2)	O2—C1—C2—N1	169.5 (2)
O1—C1—C2—N1	−12.4 (2)	O1—C1—C2—C4	106.7 (2)
O2—C1—C2—C3	52.5 (2)		

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*
O3—H3O···O1^{i}	0.90 (3)	1.75 (3)	2.623 (2)
N1—H1*A*···O1^{ii}	0.97 (3)	1.89 (3)	2.832 (3)
N1—H1*C*···O2^{iii}	0.97 (3)	1.76 (4)	2.719 (3)
N1—H1*B*···O4^{iv}	0.96 (3)	1.93 (3)	2.879 (2)

Symmetry codes: (i) $x, y, 1+z$; (ii) $-x, \frac{1}{2}+y, -z$; (iii) $x, 1+y, z$; (iv) $x, y, z-1$.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1991). Cell refinement: *TEXSAN* (Molecular Structure Corporation, 1992). Data reduction: *TEXSAN*. Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *XP* in *SHELXTL-Plus* (Sheldrick, 1991). Software used to prepare material for publication: *SHELXL93*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1018). Services for accessing these data are described at the back of the journal.

References

Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Hayashi, Y., Sekiyama, N., Nakanishi, S., Jane, D. E., Sunter, D. C., Birse, E. F., Udvarhelyi, P. M. & Watkins, J. C. (1994). *J. Neurosci.* **14**, 3370–3377.
Jane, D. E., Jones, P. L. St J., Pook, P. C.-K., Salt, T. E., Sunter, D. C. & Watkins, J. C. (1993). *Neuropharmacology*, **32**, 725–727.
Kemp, M. C., Roberts, P. J., Pook, P. C.-K., Jane, D. E., Jones, A. W., Jones, P. L. St J., Sunter, D. C., Udvarhelyi, P. M. & Watkins, J. C. (1994). *Eur. J. Pharmacol.* **266**, 187–192.
Knöpfel, T., Kuhn, R. & Allgeier, H. (1995). *J. Med. Chem.* **38**, 1417–1426.
Lehmann, M. S., Koetzle, T. F. & Hamilton, W. C. (1972). *J. Am. Chem. Soc.* **94**, 2657–2660.
Molecular Structure Corporation (1991). *MSC/AFC Diffractometer Control Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
Molecular Structure Corporation (1992). *TEXSAN. Single Crystal Structure Analysis Package*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.

Pin, J.-P. & Duvoisin, R. (1995). *Neuropharmacology*, **34**, 1–26.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1991). *SHELXTL-Plus*. Release 4.1. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (1993). *SHELXL93. Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.
Watkins, J. & Collingridge, G. (1994). *TIPS*, **15**, 333–342.

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(*E*)-3,5-Dichloro-3,5-bis(chloromethyl)-1,2,4-trioxolane

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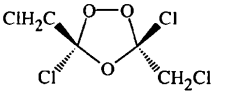
Abstract

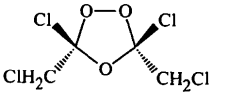
The major crystalline product derived from the ozonolysis of 1,2,3,4-tetrachlorobut-2-ene has been shown to be the monocyclic ozonide title compound, $C_4H_4Cl_4O_3$, (1), rather than the *Z* stereoisomer originally reported. The ozonide ring of (1) adopts a half-chair conformation. The molecules pack together to form sheets linked together by a series of Cl···Cl interactions.

Comment

Recently one of us has reported the first synthesis of stable ozonides derived from acyclic olefins bearing Cl atoms at the C=C double bond (Griesbaum, Schlindwein & Hilß, 1993). Ozonolysis of a solution of (*E*)-1,2,3,4-tetrachlorobut-2-ene in pentane at 233 K afforded a mixture (3:1) of two stereoisomeric ozonides which were separable by column chromatography. On the basis of the published observation that *Z* ozonides have the longer retention time in gas or column chromatography as compared with the corresponding *E* isomers (Bailey, 1978), the minor and major components have been tentatively assigned the *E* and *Z* configurations, respectively, as depicted in structural formulae (1) and (2). Since the results of subsequent HPLC analyses and substitution reactions involving isomers (1) and (2) were inconsistent, it became evident that the use of chromatographic retention times was an unreliable basis for the stereochemical assignment of the isomeric ozonides (1) and (2). An X-ray crystallographic analysis of the crystalline major component, the supposed *Z* isomer, was undertaken to resolve the structural ambiguity.



(1)



(2)

From the crystal structure determination it is clear that the tetrachloroozonide corresponding to the major component is in fact the *E* isomer, (1) (Fig. 1), contrary to the previous assignment. The title compound, (1), crystallizes with no crystallographically imposed symmetry. There is a network of significantly short Cl···Cl intermolecular contacts in the range 3.303–3.820 Å such that the molecules of (1) form infinite sheets. The shortest contacts were for Cl1···Cl1^{i} [3.303 (2) Å; symmetry code: (i) $-x, -y, 1-z$] and Cl2···Cl3^{ii} [3.364 (1) Å; symmetry code: (ii) $1-x, y-\frac{1}{2}, \frac{1}{2}-z$]. An analysis of Cl···Cl intermolecular contacts between 3.0 and 3.4 Å, where both Cl atoms are attached to C atoms, found in the Cambridge Structural Database (CSD) (Fletcher, McMeeking & Parkin, 1996; Allen & Kennard, 1993), indicates that the most frequent distance was between 3.374 and 3.384 Å (65 examples out of a total sample of 530).

The central 1,2,4-trioxolane ring of (1) adopts a half-chair conformation with approximate C_2 symmetry in which the peroxidic O1 and O2 atoms are located on either side of the plane defined by C1, O3 and C2, with the ring Cl atoms and the chloromethyl groups in pseudo-axial and equatorial positions, respectively. This conformation is quite different from that observed for the relatively few examples of monocyclic ozonides found in the CSD (Fletcher, McMeeking & Parkin,

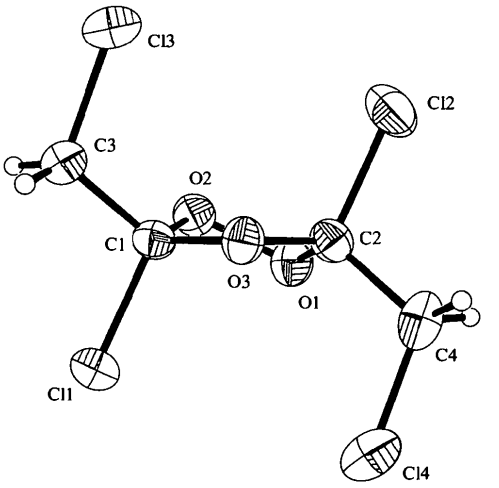


Fig. 1. Perspective view of the molecular structure of the title ozonide with 40% probability displacement ellipsoids, except for H atoms which have artificial radii of 0.1 Å for clarity.