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Camphoric acid derivatives as components of glass systems: the structure of 3-methyl (1*R*,3*S*)-(+)-camphorate

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Abstract

3-Methyl (1*R*,3*S*)-(+)-camphorate (III) has been found to have a wider potential as a component of mixed carboxylate glasses than does the parent acid, (1*R*,3*S*)-(+)-camphoric acid (I). The solution and solid-state structures of (III) have been determined by NMR (^{1}H and ^{13}C) and single crystal X-ray diffraction, respectively. Infrared spectral and optical rotation data are also presented. Each molecule is linked to two other molecules by strong intermolecular hydrogen bonds [O2···O3 = 2.716(Å)] to give chains of molecules. With care, zinc camphorate can be successfully incorporated into glass forming systems, but its scope is limited: the calcium and copper salts have no value as glass formers. © 1998 Elsevier Science B.V. All rights reserved.

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1. Introduction

As part of a study on controlled release systems, based on organic glasses, for use with a variety of drugs, we have been investigating the potential of carboxylic acids and their salts to form low temperature glasses (Blair et al., 1989, 1992, 1994; Richardson, 1996). Various carboxylic acid salts, either as single component systems or as mixtures, have been shown to form melts at low temperatures, from which glasses can be formed on fast quenching. The melts can dissolve various biologically active organic compounds, such as steroids, pheromones and biocides, without decomposition or loss of activity. The quenched glasses erode/dissolve in aqueous systems at rates which vary with the composition.

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Table 1
Standard mixed carboxylate glass systems

No.	Components[a]	Mol. ratio of components	T_m (°C)[b]	T_g (°C)[c]
1	$NaO_2CCH_3:KO_2CCH_3:Ca(O_2CCH_3)_2$	1:1:1	140	38
2	$NaO_2CC_2H_5:KO_2CC_2H_5:Ca(O_2CC_2H_5)_2$	1:1:1	125	—
3	$LiO_2CCH_3:Ca(O_2CC_2H_5)_2:NaO_2CC_7H_{15}$	1:1:1	130	49
4	$NaO_2CCH_3:Ca(O_2CC_2H_5)_2:NaO_2CC_7H_{15}$	1:1:1	—	61
5	$Zn(O_2CC_3H_7)_2:NaO_2CC_7H_{15}$	1:0.9	140	48
6	$Zn(O_2CR)_2:NaO_2CC_7H_{15}$[a]	1:1	—	25
7	$Zn(O_2CC_3H_7)_2:KO_2CC_7H_{15}$	1:1	130	—

[a] R, $CH_3CH_2CMe_2$;
[b] T_m, melt temperature;
[c] T_g, glass transition temperature.

The studies with achiral systems have been extended to derivatives of chiral carboxylic acids.

Chiral carboxylate glass systems are considered to usefully extend the application of carboxylate glasses as controlled release matrices particularly for chiral bioactive compounds. In addition, such glass systems could have potential as chromatographic materials for enantiomeric separations.

The use of readily available (1*R*,3*S*)-(+)-camphoric acid (I), its monomethyl ester 3-methyl (1*R*,3*S*)-(+)-camphorate (III), and some metal derivatives as components of low-temperature glasses have been studied. The metal derivatives include copper and organotin compounds, both metals having associated bioactivity. The crystal structure of the parent dibasic acid (I), has been published (Barnes et al., 1991) and we have prepared (III) by controlled demethylation of dimethyl camphorate (II) and determined its crystal structure. As hydrogen bonding networks are important features in the structures and properties of glasses as well as of crystalline solids, it was considered of interest to compare the hydrogen bonding situations in (I) and its monomethyl ester (III).

2. Synthesis and methods

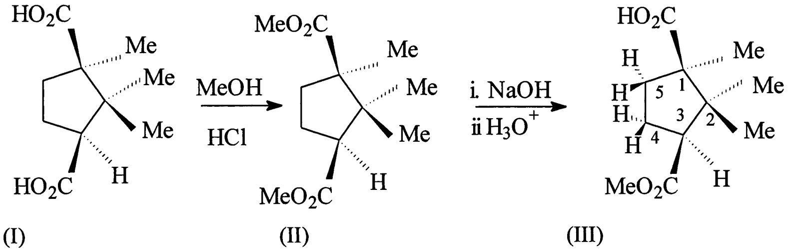
2.1. Melting points, NMR, IR, DSC, optical rotation

Melting points were measured using a Kofler hot-stage microscope and are uncorrected. NMR spectra were obtained on a Bruker 250 MHz instrument; IR spectra were recorded on Phillips Analytical PU900 and Nicolet 205 Fourier-transform instruments. Glass transition temperatures were determined on a Polymer Laboratories PL-DSC instrument. Optical rotations were measured on a Bellingham and Stanley P20 polarimeter.

2.2. Preparation of 3-methyl (1R,3S)-(+)-camphorate (Baumgarten et al., 1975)

Anhydrous HCl gas was passed through a stirred solution of (1*R*,3*S*)-(+)-camphoric acid [(1*R*,3*S*)-(+)-1,2,2-trimethyl-1,3-cyclopentanedicarboxylic acid], (I), (10.0 g, 0.050 mol.) in MeOH (125 ml) for 2 h. The solution was rotary evaporated and the residue was dissolved in 5% aqueous sodium bicarbonate solution. An aqueous solution of sodium hydroxide (2 N, 50 ml) was added. The remaining dimethyl ester, (II), was removed by extraction with diethyl ether. The aqueous layer was acidified with 10% aqueous hydrochloric acid and extracted with diethyl ether (450 ml). The ether extract was dried over magnesium sulphate and evaporated. The residue was recrystallised from petroleum ether (60–80°), yield 5.1 g, 48%.

m.p. 76–77°C, lit. (Baumgarten et al., 1975) value 77–77.5°C. Analysis. Found: C, 61.6; H, 8.4. Calculated for $C_{11}H_{18}O_4$: C, 61.7; H, 8.5%. $[\alpha]^{25} + 51.3°$ ($l = 2$, $c = 0.04$, EtOH), lit. (Baumgarten et al., 1975) value $+51.9°$ ($l = 2$, $c = 0.04$, EtOH). IR (KBr, cm^{-1}) 1700 (CO_2H), 1735



Scheme 1.

(CO_2Me). ^1H NMR ($CDCl_3$, 250 MHz) δ: 0.87(s, 3H, Me), 1.26(s, 3H, Me), 1.33(s, 3H, Me), 1.53(ddd, 1H, $J_{5A,4A} = 3.8$ Hz, $J_{5A,4B} = 9.5$ Hz, $J_{5A,5B} = 13.4$ Hz, H_{5A}), 1.84(dddd, 1H, $J_{4B,5B} = 7.5$ Hz, $J_{4B,5a} = 9.5$ Hz, $J_{H4B,3} = 10.1$ Hz, $J_{4A,4B} = 13.8$ Hz, H_{4B}), 2.24(dddd, 1H, $J_{4A,5A} = 3.8$ Hz, $J_{4A,3} = 8.7$ Hz, $J_{5B,4A} = 11.8$ Hz, $J_{4A,4B} = 13.8$ Hz, H_{4A}), 2.58(ddd, 1H, $J_{5B,4B} = 7.5$ Hz, $J_{5B,4A} = 11.8$ Hz, $J_{5A,5B} = 13.4$ Hz, H_{5B}) 2.83(dd, 1H, $J_{3,4A} = 8.7$ Hz, $J_{3,4B} = 10.1$ Hz, H_3), 3.71(s, 3H, OMe) ^{13}C NMR ($CDCl_3$, 63 MHz) δ: 21.5[Me], 21.8[Me], 23.0[Me], 23.1[C_4], 33.1[C_5], 46.7[C_2], 51.4[OMe], 53.2[C_3], 56.5[C_1], 174.5[CO_2Me], 176.8[CO_2H].

2.3. Zinc (1R,3S)-(+)-camphorate

To a solution of (1*R*,3*S*)-(+)-camphoric acid (III) (3.00 g, 0.015 mol) in H_2O (200 ml) was successively added with stirring KOH (1.68 g, 0.030 mol)) and a solution of $ZnSO_4.7H_2O$ (5.61 g, 0.020 mol) in H_2O (100 ml). The colourless precipitate of zinc (1*R*,3*S*)-(+)-camphorate was collected, washed with H_2O and acetone, and dried under vacuum overnight at 50°C. IR (KBr) 1530 cm^{-1}. m.p. > 300°C.

2.4. Calcium (1R,3S)-(+)-camphorate

Colourless calcium (1*R*,3*S*)-(+)-camphorate was prepared similarly from (1*R*,3*S*)-(+)-camphoric acid (I) (3.00 g, 0.015 mol), KOH (1.68 g, 0.030 mol) and $Ca(NO_3)_2.4H_2O$ (3.39 g, 0.018 mol). IR (KBr) 1531 cm^{-1}. m.p. > 300°C.

2.5. Copper (1R,3S)-(+)-camphorate

Deep blue coloured copper (1*R*,3*S*)-(+)-camphorate was prepared similarly from (1*R*,3*S*)-(+)-camphoric acid (I) (3.00 g, 0.015 mol), KOH (1.68 g, 0.030 mol) and $Cu(NO_3)_2.3H_2O$ (4.28 g, 0.018 mol). IR (KBr) 1597 cm^{-1}. m.p. > 300°C.

2.6. Diphenyltin (1R,3S)-(+)-camphorate

To a suspension of Ph_2SnCl_2 (4.10 g, 0.0116 mol) and (1*R*,3*S*)-(+)-camphoric acid (I) (2.32 g, 0.0116 mol) in CCl_4 (150 ml) was added with stirring Et_3N (0.80 g). After 30 min, the solvent was removed under reduced pressure to leave a colourless solid, which was recrystallised from acetone/pet.ether (60–80°).

Analysis. Found: C, 56.3; H, 5.0. Calculated for $C_{22}H_{24}O_4Sn$: C, 56.1; H, 5.1%. IR (KBr) 1545 cm^{-1}. m.p. 135–136°C.

2.7. Zinc 3-methyl (1R,3S)-(+)-camphorate

To a stirred solution of KOH (0.785 g, 0.014 mol) in H_2O (150 ml) was successively added 3-methyl (1*R*,3*S*)-(+)-camphorate (I) (3.0 g, 0.014 mol) and a solution of $ZnSO_4.7H_2O$ (5.24 g, 0.023 mol) in H_2O (50 ml). The white precipitate was collected, washed with H_2O, and dried under vacuum overnight at 50°C. IR (KBr) 1577, 1705 cm^{-1}. m.p. > 250°C.

Table 2
Comparison of solution ^3J(H–H) NMR values with values calculated from solid state (X-ray data) torsion angles

Angle	Torsion angle	Solid state calculated[a] ^3J(H–H) Hz	Solution (in $CDCl_3$) ^3J(H–H) Hz
H3–C3–C4–H4A	−21.4	9.0	8.7
H3–C3–C4–H4B	−141.3	7.8	10.1
H4A–C4–C5–H5B	−10.7	9.9	11.8
H4B–C4–C5–H5B	−130.6	6.2	7.5
H4A–C4–C5–H5A	109.8	2.6	3.8
H4B–C4–C5–H5A	−10.1	9.9	9.5

[a] Calculated from the Haasnoot et al. (1980) equation.

2.8. Single crystal X-ray diffraction

X-ray data were collected on a Delft Instruments FAST diffractometer. The structure was solved by direct methods using SIR92 (Altomare et al., 1994) and refined with SHELXL-97 (Sheldrick, 1997). The non-hydrogen atoms were refined with anisotropic displacement parameters and the hydrogen atoms with isotropic displacement parameters. The coordinates of H2 (involved in hydrogen bonding) were refined but other hydrogens were only allowed to ride on their attached carbon atoms.

2.9. Glass preparation

A general procedure used to prepare mixed component glasses involved mixing appropriate amounts of the materials, grinding the mix to a fine dust, applying the lowest heat necessary to melt the mix, and quenching the melt as quickly as possible in a cooled brass mould and pressing with an aluminium stamp. An alternative procedure, used in particular with high melting carboxylates, was to add the higher melting component to a melt of the lower melting component(s) in order to minimise thermal decompositions. If a bioactive was to be incorporated into the matrix, this would be done just prior to quenching the molten glass former and in a manner to minimise the contact time at the melt temperature. The melt temperatures varied with the component mix but were generally lower than 140°C. Contact with air was kept to a minimum during the melt, incorporation and quenching stages. The amount of incorporation varied between 2 and 30%. Assays were always made of the efficiency of the incorporation and of any decomposition.

Various mixed carboxylate systems have been shown, from earlier studies, to be good glass formers; the systems listed in Table 1 were used to assess the abilities of the camphorate derivatives to act as components of glass systems.

3. Results and discussion

3.1. Synthesis

The title compound (III) was prepared as shown in Scheme 1, without any attempt to purify the dimethyl camphorate intermediate, (II).

3.2. Solution NMR spectrum

The complete assignment of the 250 MHz ^1H NMR spectrum of (III) in $CDCl_3$ solution and determination of all J(H–H) coupling constants was achieved.

The ^3J(H–H) coupling constants, associated with the ring carbon atoms in (III) and measured in $CDCl_3$ solution, are listed in Table 2; these values can be compared with the values calculated from the solid state H–C–C–H torsion angles and the Haasnoot et al. (1980) modification of the Karplus equation, Eq. (1). The comparison indicates that only a little conformational change occurs on dissolution.

Table 3
Crystal data and structure refinement

Empirical formula	$C_{11}H_{18}O_4$
Formula weight	214.25
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	$a = 7.1610(7)$ Å $b = 10.9960(5)$ Å $c = 14.497(3)$ Å $\alpha = 90°$ $\beta = 90°$ $\gamma = 90°$
Volume	1141.5(3) Å^3
Z	4
Density (calculated)	1.247 Mg/m^3
Absorption coefficient	0.094 mm^{-1}
$F(000)$	464
Crystal size	0.30 × 0.30 × 0.10 mm
θ range for data collection	2.32–24.89°
Index ranges	$-8 \leq h \leq 4$ $-12 \leq k \leq 11$ $-15 \leq l \leq 15$
Reflections collected	4160
Independent reflections	1739 [R(int) = 0.1071]
Observed reflections [$(I > 2\sigma(I)$]	1486
Max. and min. transmission	0.9907 and 0.9724
Refinement method	Full-matrix l.s. on F^2
Number of parameters	145
Goodness-of-fit on F^2 (S)	0.959
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0396$, $wR_2 = 0.0884$
R indices (all data)	$R_1 = 0.0454$, $wR_2 = 0.0901$
Final weighting scheme	calc $w = 1/[\sigma^2(F_o^2) + (0.0251P)^2]$, where $P = (F_o^2 + 2F_c^2)/3$
Residual diffraction max.	0.208 e/Å^3
Residual diffraction min.	−0.176 e/Å^3

Table 4
Atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 × 10^3)

Atom	x	y	z	U(eq)
O(1)	7150(2)	1429(2)	1100(1)	44(1)
O(2)	5657(3)	−336(1)	1278(1)	41(1)
O(3)	1229(2)	3255(1)	3747(1)	29(1)
O(4)	−792(2)	1763(1)	3443(1)	32(1)
C(1)	3776(3)	1436(2)	1280(2)	26(1)
C(2)	2893(3)	1228(2)	2261(2)	23(1)
C(3)	1318(3)	2218(2)	2260(2)	24(1)
C(4)	2150(3)	3309(2)	1729(2)	32(1)
C(5)	3848(3)	2841(2)	1201(2)	32(1)
C(6)	4354(3)	1469(2)	3012(2)	28(1)
C(7)	2047(4)	−42(2)	2411(2)	36(1)
C(8)	5715(4)	880(2)	1207(2)	29(1)
C(9)	2568(3)	920(2)	492(2)	38(1)
C(10)	629(3)	2499(2)	3210(2)	24(1)
C(11)	−1555(4)	1921(2)	4360(2)	40(1)

U(eq) is defined as one third of the trace of the orthogonalised U_{ij} tensor.

$$^3J(\mathrm{H{-}H}) = 13.86 \cos^2 \phi - 0.81 \cos \phi + \sum \Delta\chi_i \{0.56 - 2.32 \cos 2(\zeta_i \phi + 17.9 \Delta\chi_1)\} \quad (1)$$

$\zeta = \pm 1$; $\Delta\chi$ = electronegativity difference between ith atom and H.

3.3. Crystallography

Details of the crystal data and structure refinement are given in Table 3 and the atom coordinates are listed in Table 4. Further details (bond lengths, valency angles, torsion angles, anisotropic thermal displacements and hydrogen positions are available in supplementary material).

The atomic arrangement in the molecule was obtained with program ZORTEP (Zsolnai, 1997) and is shown in Fig. 1.

The 5-membered ring adopts a half-chair conformation with puckering parameters $Q(2) = 0.426$ Å and $\Phi(2) = 202.3°$ (Cremer and Pople, 1975). The hydrogens about the C3–C4 and C4–C5 bonds are more staggered than eclipsed.

Intermolecular hydrogen bonding is present with O(2)···O(3)* = 2.716(2) Å (* indicates coordinates transposed by $1-x$, $-0.5+y$, $0.5-z$). The hydrogen bonds involve the carbonyl hydrogen of one molecule and the ester carbonyl group of an adjacent molecule and so link the molecules into chains. Here O(2)–H(2) = 0.95(3) Å, O(3)···H(2) = 1.80(3) Å and O(2)–H(2)···O(3) = 161(2)°. A crystal packing diagram was obtained with program CAMERON (Watkins et al., 1993) and is shown in Scheme 2 (the intermolecular hydrogen bonding is denoted by dotted lines).

The structure of (1*R*,3*S*)-(+)-camphoric acid (I) (Barnes et al., 1991), has been reported in both monoclinic and orthorhombic crystal forms—here the two carboxylic acid groups enable each camphoric acid molecule to be linked to two other molecules by four hydrogen bonds. Whereas the molecular chains in the monoclinic form are normal the chains in the orthorhombic form of camphoric acid show some disorder. Hence the hydrogen bonding in (1*R*,3*S*)-(+)-camphoric acid (I) is more extensive than that in 3-methyl (1*R*,3*S*)-(+)-camphorate (III).

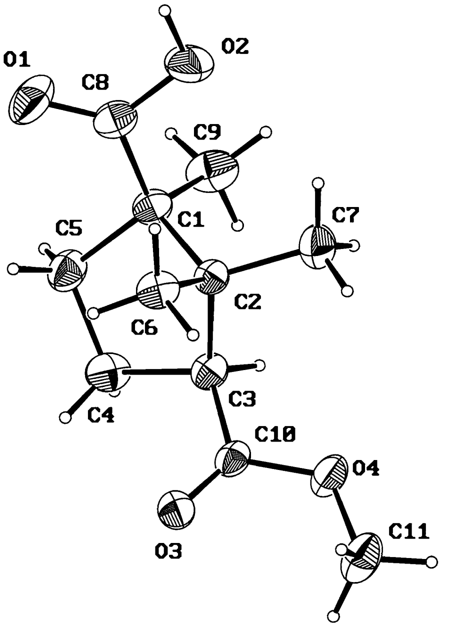


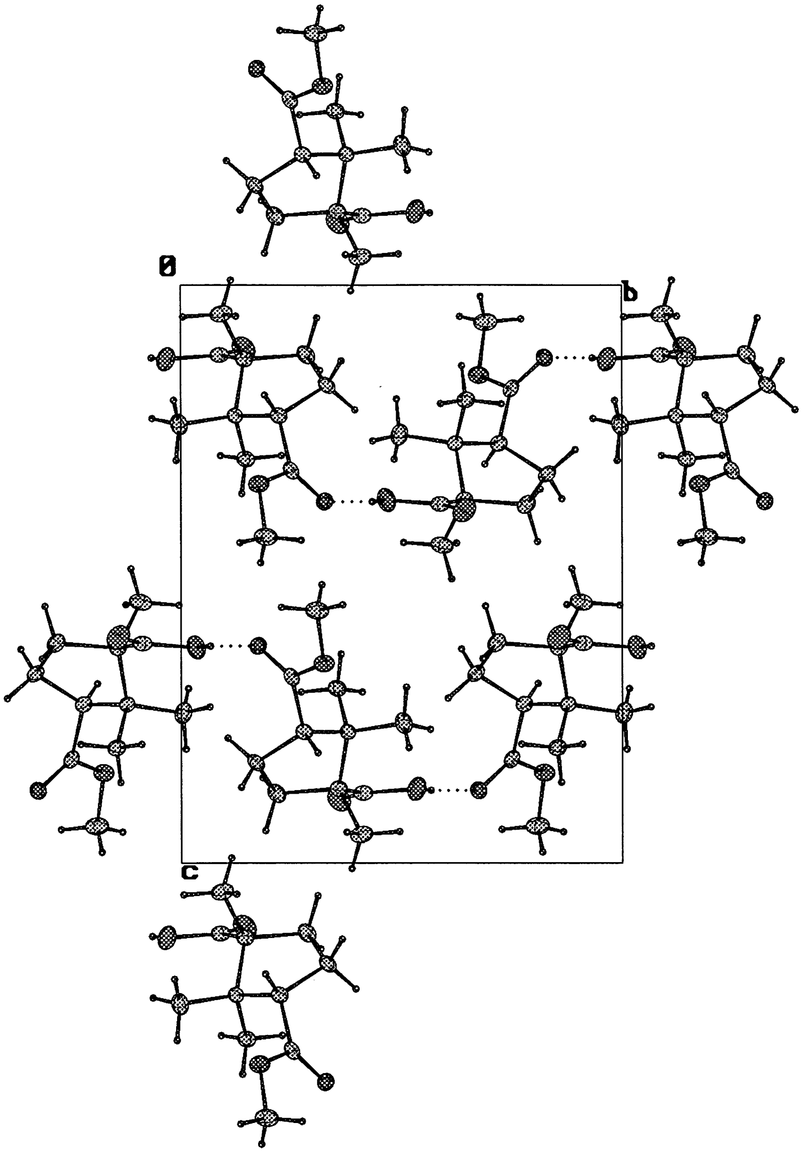
Fig. 1. The atomic arrangement in 3-methyl (1*R*,3*S*)-(+)-camphorate. Thermal ellipsoids shown at the 50% probability level.

3.4. Glass formations and properties

(1*R*,3*S*)-(+)-Camphoric acid (I) alone forms a glass on quenching its melt, moreover its utility is heightened by its use as a component (up to 50%) of a mixed carboxylate system containing lower metal carboxylates, i.e. carboxylates with less than six carbon atoms. These glasses containing (1*R*,3*S*)-(+)-camphoric acid were transparent and showed no sign of decomposition; however they did have a tendency to crack if not quenched quickly in a uniform fashion. Attempts to add (1*R*,3*S*)-(+)-camphoric acid (I) to higher carboxylates generally resulted in severe decomposition occurring.

3-Methyl (1*R*,3*S*)-(+)-camphorate (III) has a much lower m.p. than does (1*R*,3*S*)-(+)-camphoric acid (I) (77°C compared with 186°C) and for this reason could be a more useful component of a mixed carboxylate glass system. Additionally, 3-methyl (1*R*,3*S*)-(+)-camphorate (III) readily dissolves in all the melts used without decomposition and clearly has much potential as a glass former. As generally found for mixed carboxylate systems, the melts containing 3-methyl (1*R*,3*S*)-(+)-camphorate (III) were shown to allow safe dissolution of various organic compounds, such as steroids and melatonin.

Zinc (1*R*,3*S*)-(+)-camphorate, although polymeric in nature, and with a melting point in excess of 300°C, could be safely incorporated into a few mixed metal carboxylate glasses, for example, up to 50% into a pre-formed $Zn(O_2CC_3H_7)_2$:$NaO_2C_7H_{15}$ (1:0.9 mol. ratio) system. However, the successful incorporation required much care and was far from easy to achieve on other than a small scale. Further problems were experienced with calcium (1*R*,3*S*)-(+)-camphorate. Only a very small amount of calcium (1*R*,3*S*)-(+)-camphorate could be added to any mixed metal carboxylate melt if workable materials were to be obtained. Addition of the calcium salt lead to a substantial increase in melt viscosities and difficulties in obtaining completely homogeneous solutions. Even with low levels of incorporation of calcium (1*R*,3*S*)-(+)-camphorate, the resulting glasses devitrified very soon after preparation.



Scheme 2. A crystal packing diagram of 3-methyl (1*R*,3*S*)-(+)-camphorate viewed down the *a* axis. Intermolecular H-bonding between H2 and O3 is shown as a dotted line.

Copper carboxylates, such as the butanoate, have been found to form successful glasses with potassium carboxylates: these glasses have a very attractive deep blue colour. Unfortunately, copper (1*R*,3*S*)-(+)-camphorate could not be successfully added to any pre-formed melt: even trace amounts led to instant decomposition of the melts with the liberation of copious amounts of a gas. Generally, the melts hardened to an intractable black crust.

Diphenyltin (1*R*,3*S*)-(+)-camphorate did not dissolve in any of the melts tried; however, prolonged heating at the melt temperatures to encourage dissolution did not lead to decomposition. Previous studies with other organotin compounds indicated that up to 5% incorporation into acetate glasses was possible (Blair et al., 1990).

As zinc 3-methyl (1*R*,3*S*)-(+)-camphorate has a lower m.p. than zinc camphorate (140°C compared with >300°C), it was considered to have an even greater potential as a glass former. However, this monoester salt would not dissolve in any of the standard melts. In most cases, a white suspension was produced, although no decomposition was apparent.

4. Conclusion

The structure of the mono-methyl ester of camphoric acid (III) obtained by base-catalysed demethylation of dimethyl camphorate has been confirmed as 3-methyl (1*R*,3*S*)-(+)-camphorate. In the solid state, molecules of 3-methyl (1*R*,3*S*)-(+)-camphorate are linked into chains via hydrogen bonds. The hydrogen bonding is considered to persist in the glass state of (I) and will play a significant role in determining the glass properties of (III).

3-Methyl (1*R*,3*S*)-(+)-camphorate (III) has been found to have a wider potential as a component of mixed carboxylate glasses than does the parent acid, (1*R*,3*S*)-(+)-camphoric acid (I). With care, zinc camphorate can be successfully incorporated into glass forming systems, but its scope is limited: the calcium and copper salts have no value as glass formers.

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