Optical Resolution of Amino Acid and Hydroxycarboxylic Acid Esters by Complexation with Optically Active Host Compounds: a Crystallographic Result

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Selected esters derived from amino and hydroxycarboxylic acids have been resolved by inclusion complexation with optically active host compounds derived from tartaric acid. The crystal structure of the inclusion compound **I** (*R,R*)-(−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]-nonane·½(methyl 3-hydroxybutanoate) is reported. **I** $[(C_{33}H_{32}O_4)_2\cdot C_5H_{10}O_3]$ is monoclinic $P2_1$, $a = 9.176(2)$, $b = 39.70(2)$, $c = 9.216(2)$ Å, $\beta = 119.45(1)°$, $V = 2923(2)$ Å^3. The structure was solved by direct methods and refined to a final R value of 0.037. Host and guest molecules are linked by hydrogen bonding.

Inclusion compounds have been extensively studied for their properties of storing or separating guest compounds.[1] The process is one of molecular recognition in which host molecules and guest molecules interact and form a new compound of distinct stoichiometry which may be a molecular complex or a true clathrate, depending on the kind of molecular interaction. The classification of host–guest compounds has been discussed by Weber,[2] while their use for resolving optical isomers has been reviewed by Toda.[3]

The design of the chiral host *trans*-4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane has been described by Toda and Tanaka[4] and we have elucidated the structures obtained with this host compound and two resolved bicyclic enones.[5]

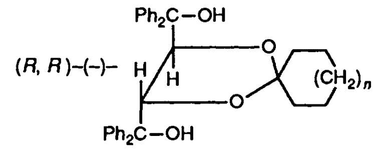
Experimental

The esters methyl 2-aminopropanoate (**2**), methyl 2-amino-3-phenylpropanoate (**3**) and ethyl 2-amino-2-phenylethanoate (**4**), and esters of hydroxycarboxylic acids such as methyl 3-hydroxybutanoate (**5**), ethyl 3-hydroxybutanoate (**6**), methyl 4-chloro-3-hydroxybutanoate (**7**), and dimethyl 2-hydroxybutanedioate (**8**) were resolved by complexation with the following optically active host compounds; (*R,R*)-(−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonane (**1a**)[6] and (*R,R*)-(−)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[5.4]decane (**1b**).[7]

One example of the resolution of the amino acid esters and of the hydroxycarboxylic acid is described. To a solution of **1b** (10.87 g, 21.5 mmol) and racemic-**2** (4.43 g, 43.0 mmol) in benzene (9 cm^3) light petroleum, b.p. 60–80 °C, (9 cm^3) was added and the solution kept at room temperature for 4 h. This yielded a 2:1 inclusion complex of **1b** and (+)-**2** which after three recrystallizations from benzene–light petroleum (1:1) gave colourless crystals (1.51 g, 13%), m.p. 195–197 °C, $[\alpha]_D$ −57.6 (*c* 0.5, $CHCl_3$). Heating the complex *in vacuo* gave (−)-**2** of 100% ee by distillation (0.13 g, 12%, $[\alpha]_D$ +7.4 (*c* 0.5, MeOH). The optical purity was determined by ^1H NMR spectroscopy by using $Eu(hfc)_3$ as a chiral shift reagent.

Using a similar procedure, **3** and **4** were also resolved, although the resolution of **4** was not efficient. The results are shown in Table 1. However the reason why the resolution of **2** and **3** is effected by the hosts **1b** and **1a**, respectively, is not clear.

Optical resolution of **5** was carried out as follows: to a solution of **1a** (7.09 g, 14.4 mmol) and *rac*-**5** (1.67 g, 14.14 mmol) in ether (45 cm^3) was added light petroleum (35 cm^3), and the solution was kept at room temperature for 22 h. This gave a 2:1 inclusion complex of **1a** and (+)-**5**, which after one recrystallization from ether–light petroleum (1:1) yielded crystals {3.60 g, 45.3%, m.p. 134–159 °C, $[\alpha]_D$ −26.1 (*c* 0.5, $CHCl_3$)}. Heating of the complex *in vacuo* gave (+)-**5** of 100% ee by distillation [0.37 g, 44%, $[\alpha]_D$ +49.8 (*c* 0.5, $CHCl_3$)]. The optical purity was determined for *ortho*-benzoate by HPLC using a column containing an optically active solid phase, Chiralcel OB (from Daicel Industries). By a similar procedure, **6**–**8** were resolved (Table 1). Although the resolution of **6** with **1a** is effective, the resolutions of **7** and **8** are not very good. The reason why **1a** is effective for the resolution of **5**–**7**, but not for **8** is again not clear. In order to understand the mechanism of the efficient chiral recognition between **1a** and (+)-**5**, the structure of their 2:1 complex, compound **I**, was studied by X-ray analysis.



1

a: $n = 0$
b: $n = 1$

$MeCH(NH_2)COOMe$ **2**

$PhCH_2CH(NH_2)COOMe$ **3**

$PhCH(NH_2)COOEt$ **4**

$MeCH(OH)CH_2COOMe$ **5**

$MeCH(OH)CH_2COOEt$ **6**

$ClCH_2CH(OH)CH_2COOMe$ **7**

$MeOOCCH_2CH(OH)COOMe$ **8**

Scheme 1

X-Ray Analyses.—A suitable single crystal was selected and irradiated with MoKα ($\lambda = 0.7107$ Å) radiation on an Enraf-Nonius CAD4 diffractometer. Accurate cell parameters were obtained by least-squares refinement on the setting angles of 24 reflections ($16 \leqslant \theta \leqslant 17°$). Transformations [100 001 010] and [100 010 102] to apparently hexagonal and orthorhombic cells were checked for the required equivalences (6/*m*, 6/*mmm*; *mmm* symmetries respectively); no such equivalences were found and the monoclinic cell retained. Owing to the long *b* axis, the data were collected in the ω mode, with variable scan width, aperture width and scan speed, with a maximum

Table 1 Optical resolution by complexation with **1a** and **1b**

	Optical resolution by **1a**		Optical resolution by **1b**	
Guest	Yield (%)	Optical purity (% ee)	Yield (%)	Optical purity (% ee)
2	—	—[a]	+12	100[b]
3	+40	100[b]	+86	17[b]
4	−63	2[b]	−65	6[b]
5	+44	100[c]	—	—[a]
6	+28	100[d]	—	—[a]
7	+15	64[e]	—	—[a]
8	—	—[a]	+45	40[f]

[a] No complexation occurred. [b] Optical purity was determined by ^1H NMR spectroscopy by using $Eu(hfc)_3$ as a chiral shift reagent. [c] Optical purity was determined for *ortho*-benzoate by HPLC using a column containing an optically active solid phase, Chiralcel OB. [d] Optical purity was determined by comparing the $[\alpha]_D$ value with that reported (D. Seebach and M. F. Zuger, *Org. Synth., Coll. Vol.*, **63**, 1984). [e] Optical purity was determined by comparing the $[\alpha]_D$ value with that reported (D. Seebach and M. F. Zuger, *Angew. Chem., Int. Ed. Engl.*, 1984, **2**, 151). [f] Optical purity was determined by comparing the $[\alpha]_D$ value with that reported (F. Toda and K. Tanaka, *Tetrahedron Lett.*, 1988, **29**, 1807).

Table 2 Crystal data, details of the data collection and final refinement for **I**

	I
Molecular formula	$(C_{33}H_{32}O_4)_2 \cdot C_5H_{10}O_3$
Host:guest	2:1
Space group	$P2_1$
a/Å	9.176(2)
b/Å	39.70(2)
c/Å	9.216(2)
β/°	119.45(1)
V/Å^3	2923(2)
D_c/g cm^{-3}	1.25
F(000)	1176
μ/(MoKα)/cm^{-1}	0.78
Crystal size/mm	0.43 × 0.47 × 0.50
Scan mode	ω
θ range scanned/°	1–25
Crystal decay (%)	4
No. unique reflections collected	4772
No. observed reflections with $I_{rel} > 2\sigma I_{rel}$	4076
No. parameters, N_p	760
$R = \Sigma\|\|F_o\| - F_c\|\|/\Sigma\|F_o\| = \Sigma\|\Delta\|/\Sigma\|F_o\|$	0.037
$R_w = \Sigma w^{\frac{1}{2}}\|\Delta\|/\Sigma w^{\frac{1}{2}}\|F_o\|$	0.035
w	$(\sigma^2 F)^{-1}$
$S = (\Sigma\|\Delta\|^2/N - N_p)^{\frac{1}{2}}$	1.19
U_{iso}(hydrogens)/Å^2	0.081(2)
Max./min. residual electron density (e Å^{-3})	0.19/−0.16

Table 3 Fractional atomic coordinates (× 10^4) with esd in parentheses for **I**

Atom	x/a	y/b	z/c
C(1)	1 148(4)	4 803(0)	5 029(4)
C(111)	−279(4)	4 980(1)	3 524(4)
C(112)	−1 826(4)	4 837(1)	2 513(4)
C(113)	−3 088(5)	5 019(1)	1 230(5)
C(114)	−2 810(5)	5 348(1)	957(5)
C(115)	−1 272(6)	5 495(1)	1 949(5)
C(116)	−31(5)	5 312(1)	3 218(4)
C(121)	2 779(4)	4 820(1)	4 993(4)
C(122)	2 796(5)	4 770(1)	3 508(4)
C(123)	4 280(5)	4 753(1)	3 473(6)
C(124)	5 770(5)	4 784(1)	4 927(7)
C(125)	5 790(5)	4 840(1)	6 400(6)
C(126)	4 297(4)	4 861(1)	6 443(5)
O(1)	1 375(3)	4 975(1)	6 515(3)
C(2)	699(4)	4 433(1)	5 209(4)
O(2)	420(3)	4 242(1)	3 787(2)
C(21)	1 364(4)	3 933(1)	4 315(4)
C(22)	2 903(4)	3 930(1)	4 096(4)
C(23)	3 267(4)	3 556(1)	4 136(5)
C(24)	1 555(5)	3 400(1)	3 156(7)
C(25)	331(4)	3 631(1)	3 306(4)
C(3)	2 043(4)	4 226(1)	6 698(4)
O(3)	1 784(2)	3 897(1)	6 006(2)
C(4)	1 957(4)	4 219(1)	8 330(4)
O(4)	2 514(3)	4 541(1)	9 090(3)
C(411)	3 261(4)	3 966(1)	9 527(4)
C(412)	4 810(4)	4 072(1)	10 726(4)
C(413)	5 993(4)	3 846(1)	11 801(5)
C(414)	5 648(5)	3 509(1)	11 698(5)
C(415)	4 124(5)	3 398(1)	10 511(5)
C(416)	2 909(5)	3 623(1)	9 434(5)
C(421)	244(5)	4 141(1)	8 149(4)
C(422)	−96(5)	4 262(1)	9 365(4)
C(423)	−1 568(5)	4 179(1)	9 353(5)
C(424)	−2 744(5)	3 978(1)	8 123(5)
C(425)	−2 423(4)	3 860(1)	6 904(5)
C(426)	−947(4)	3 935(1)	6 923(4)
C(1′)	828(4)	1 576(1)	5 268(4)
C(111′)	−702(4)	1 410(1)	3 796(4)
C(112′)	−1 679(4)	1 565(1)	2 277(4)
C(113′)	−2 967(4)	1 393(1)	952(5)
C(114′)	−3 300(5)	1 063(1)	1 158(5)
C(115′)	−2 334(5)	902(1)	2 658(5)
C(116′)	−1 044(4)	1 076(1)	3 969(5)
C(121′)	817(4)	1 527(1)	6 894(4)
C(122′)	−659(4)	1 562(1)	6 963(5)
C(123′)	−686(5)	1 541(1)	8 435(5)
C(124′)	770(6)	1 477(1)	9 891(5)
C(125′)	2 247(5)	1 437(1)	9 876(5)
C(126′)	2 273(4)	1 459(1)	8 382(4)
O(1′)	2 302(3)	1 430(1)	5 338(3)
C(2′)	990(4)	1 954(1)	4 924(4)
O(2′)	−456(2)	2 132(1)	4 696(3)
C(21′)	48(4)	2 437(1)	5 653(4)

recording time of 40 s. Three reference reflections were periodically monitored for intensity and orientation control. The data were corrected for Lorentz-polarization effects but not for absorption. Further details of the crystal and data collection are reported in Table 2.

Structure solution and refinement. The structure **I** was solved by direct methods using SHELXS-86[8] and refined using SHELX-76.[9] There are two host molecules and one guest in the asymmetric unit. Owing to the large number of atoms, blocked-matrix refinement of parameters was employed. All non-hydrogen atoms were treated anisotropically, all hydrogens isotropically with a single temperature factor; hydrogens of –CH and $-CH_2$ groups were placed in calculated positions and $-CH_3$ groups were treated as rigid groups. Hydroxy hydrogens were located in the penultimate difference map and constrained to ride at 1.00(2) Å from their parent oxygens. A weighting scheme, $(\sigma^2 F)^{-1}$ was applied and maximum parameter shift/esd was <0.1. The maximum/minimum residual electron density was 0.19/−0.16 e Å^{-3}. Complex neutral atom scattering factors were taken from Cromer and Mann[10] for non-hydrogen atoms and from Stewart, Davidson and Simpson[11] for H, with dispersion corrections from Cromer

Table 3 *continued*

Atom	*x*/*a*	*y*/*b*	*z*/*c*
C(25′)	−964(4)	2 741(1)	4 654(4)
C(24′)	−1 135(7)	2 963(1)	5 875(6)
C(23′)	−199(6)	2 804(1)	7 553(5)
C(22′)	−168(4)	2 430(1)	7 178(4)
C(3′)	2 463(4)	2 153(1)	6 302(4)
O(3′)	1 749(3)	2 482(1)	6 080(3)
C(4′)	4 136(4)	2 169(1)	6 261(4)
O(4′)	4 911(3)	1 848(1)	6 837(3)
C(411′)	5 302(4)	2 427(1)	7 560(4)
C(412′)	6 563(5)	2 318(1)	9 084(4)
C(413′)	7 614(5)	2 548(1)	10 267(5)
C(414′)	7 402(5)	2 883(1)	9 954(5)
C(415′)	6 172(5)	2 995(1)	8 452(5)
C(416′)	5 121(5)	2 768(1)	7 250(5)
C(421′)	3 963(4)	2 245(1)	4 547(4)
C(422′)	5 101(4)	2 103(1)	4 156(5)
C(423′)	5 071(5)	2 176(1)	2 680(5)
C(424′)	3 887(5)	2 392(1)	1 548(5)
C(425′)	2 735(5)	2 536(1)	1 903(5)
C(426′)	2 768(5)	2 462(1)	3 392(4)
C(5)	1 632(6)	530(1)	2 924(6)
O(5)	1 261(3)	365(1)	3 779(4)
O(51)	744(5)	538(1)	1 283(5)
C(51)	−741(8)	328(2)	476(7)
C(6)	3 143(6)	759(1)	3 588(7)
C(7)	4 345(6)	721(1)	5 413(7)
O(7)	3 536(4)	800(1)	6 369(4)
C(71)	5 811(6)	951(1)	5 973(9)

and Liberman.[12] Molecular parameters were calculated using PARST[13] and drawings obtained using PLUTO.[14] All computations were performed at the Computer Centre of the University of Cape Town on a VAX 6230 computer. Further details of the data collection, structure solution and refinement are given in Table 2.

Thermal Analysis.—Differential scanning calorimetry (DSC) and thermogravimetry (TG) were performed using a Perkin-Elmer PC7 Series system. Crushed samples of approximately 5 mg weight were used. The temperature range was 50–200 °C at a heating rate of 10 °C min^{-1}. A constant stream of nitrogen flowing at 40 cm^3 min^{-1} was passed over the sample.

Results and Discussion

Final fractional atom coordinates are reported in Table 3. Perspective views of a host molecule and a guest molecule with the atomic numbering are depicted in Fig. 1. The molecular complex has a host:guest ratio of 2:1 with two hosts and one guest in the asymmetric unit. Selected bond lengths and angles are reported in Table 4. They all lie within the normally expected ranges and require no discussion. Torsion angles for the two independent host molecules differ by fewer than 5° and hence both host molecules have conformations which are essentially similar. There is molecular association *via* hydrogen bonding as reported in Table 5. For each of the host molecules, one hydroxy group is intramolecularly hydrogen bonded while the others form intermolecular hydrogen bonds with acceptor oxygens on the guest, yielding a 'trimer' of two hosts and one guest. The donor hydroxy group on the guest O(7)–H(71) has no close contacts with acceptor oxygens on either host molecule; it is closest to O(5) of the guest, at 2.853 Å, with O–H ··· O 121(3)°. The deviation of these values from usual O–H ··· O hydrogen bonding parameters may mean that the hydroxy group of the

Table 4 Selected bond lengths (Å) and angles (°) for **I**

Host		Guest	
Bond lengths/Å			
C–C$_{\text{(aryl ring)}}$	1.367(9)–1.394(6)	C(5)–O(5)	1.196(7)
C–C$_{\text{(alkyl ring)}}$	1.495(6)–1.528(6)	C(5)–O(51)	1.319(6)
C–O$_{\text{(terminal)}}$	1.426(5)–1.451(5)	C(5)–C(6)	1.513(7)
C–O$_{\text{(bonded)}}$	1.417(4)–1.441(5)	O(51)–C(51)	1.453(8)
C$_{\text{alkyl}}$–C$_{\text{aryl}}$	1.515(6)–1.540(4)	C(6)–C(7)	1.498(7)
C$_{\text{alkyl}}$–C$_{\text{alkyl}}$	1.541(4)–1.556(6)	C(7)–O(7)	1.438(9)
		C(7)–C(71)	1.492(7)
Bond angles/°			
C$_{\text{aryl}}$–C$_{\text{aryl}}$–C$_{\text{aryl}}$	117.4(4)–121.9(4)	O(51)–C(5)–C(6)	112.1(5)
C$_{\text{aryl}}$–C$_{\text{alkyl}}$C$_{\text{aryl}}$	110.0(3)–111.9(3)	O(5)–C(5)–C(6)	124.3(5)
C$_{\text{alkyl}}$–C$_{\text{alkyl}}$–C$_{\text{alkyl ring}}$	102.2(4)–108.1(4)	O(5)–C(5)–O(51)	123.5(5)
C$_{\text{alkyl}}$–C$_{\text{alkyl}}$–C$_{\text{alkyl chain}}$	117.2(3)–118.5(3)	C(5)–O(51)–C(51)	118.0(5)
C$_{\text{aryl}}$–C$_{\text{alkyl}}$–C$_{\text{alkyl}}$	108.4(3)–116.1(3)	C(5)–C(6)–C(7)	114.6(5)
C$_{\text{aryl}}$–C$_{\text{aryl}}$–C$_{\text{alkyl}}$	117.8(3)–124.4(4)	C(6)–C(7)–C(71)	111.5(5)
C$_{\text{aryl}}$–C$_{\text{alkyl}}$–O	105.6(3)–111.5(3)	C(6)–C(7)–O(7)	110.5(5)
C$_{\text{alkyl}}$–C$_{\text{alkyl}}$–O	101.3(3)–113.9(4)	O(7)–C(7)–C(71)	107.7(5)
C$_{\text{alkyl}}$–O–C$_{\text{alkyl}}$	106.8(4)–109.7(2)		
O–C$_{\text{alkyl}}$–O	104.5(3)–104.8(3)		

Table 5 Hydrogen bonding in **I**

I	O ··· O/Å	O–H/Å	H ··· O/Å	O–H ··· O/°	Symmetry op.
O(1), H(1), O(5)	2.771(5)	0.97(3)	1.81(4)	170(3)	$-x, y + 0.5, -z + 1$
O(1′), H(1′), O(7)	2.721(5)	0.97(2)	1.80(2)	159(3)	x, y, z
O(4), H(4), O(1)	2.693(1)	0.98(3)	1.73(3)	167(3)	x, y, z
O(4′), H(4′), O(1′)	2.670(4)	0.95(3)	1.77(3)	156(3)	x, y, z
O(7), H(71), O(5)	2.853(5)	0.96(3)	2.25(4)	121(3)	x, y, z

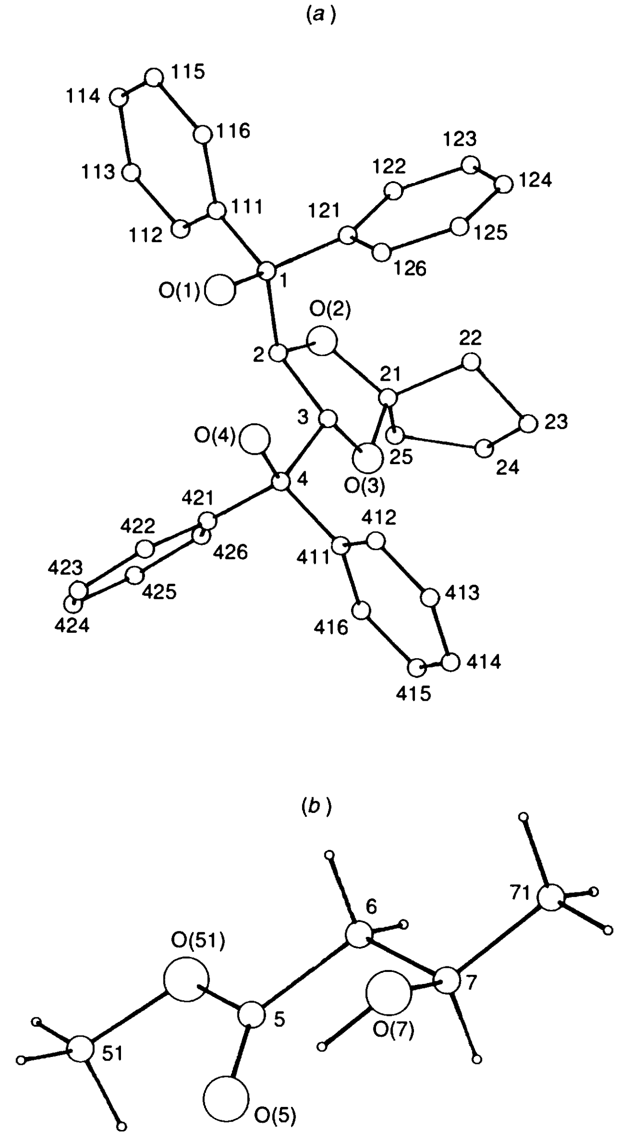


Fig. 1 Perspective view of (*a*) the host **I**; and (*b*) the guest **5**, with atomic numbering

guest molecule does not participate in the hydrogen bonding scheme. A view of the unit cell down the *c* axis is illustrated in Fig. 2, in which the hydrogen bonding is depicted with dashed lines. The results of the thermal analysis are shown in Fig. 3. The TG curve shows an experimental weight loss of 10.6%, in excellent agreement with the calculated value of 10.7%, thus confirming the host to guest ratio of 2:1 adopted in the solution of the crystal structure. The DSC curve shows three endotherms: peak A, with onset temperature at 128 °C corresponding to the guest-loss reaction, followed by peak B, which we attribute to a phase change which occurs between 155 and 165 °C, while the third peak C is due to the melting of the host compound. We have observed a similar decomposition pattern in the thermal analysis of the host 1,1,2,2-tetraphenylethane-1,2-diol which forms inclusion compounds with lutidines.[15]

In conclusion, the close association between host and guest as evidenced by the hydrogen bonding and guest release at 128 °C (a temperature much higher than the b.p. of **5** (76–77 °C) allows one to consider the inclusion complex as essentially a single molecule and hence the resolution of **5** may be likened to a diastereoisomerization process.

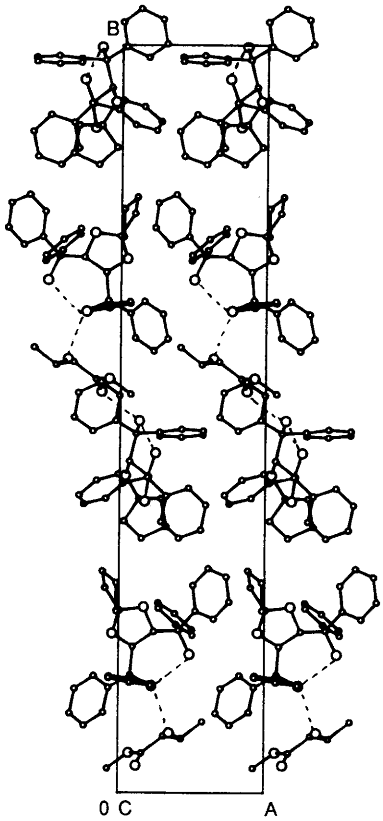


Fig. 2 Projection of the structure down the *c* axis

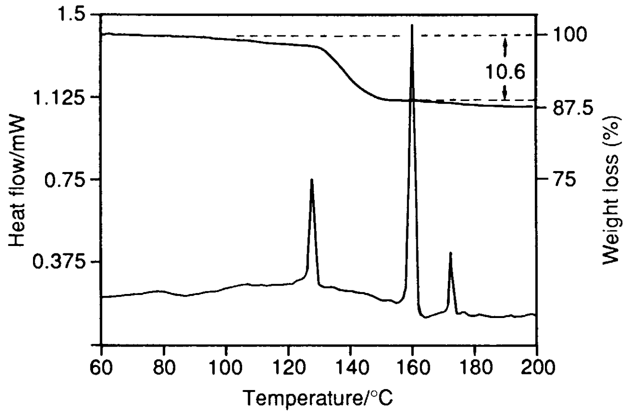


Fig. 3 Results of the thermal analysis

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