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The Absolute Configurations of *Anti*-Benzene and *Anti*-Naphthalene 1,2:3,4-Dioxides

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Summary Optically active anti-1,2:3,4-dioxides of benzene and naphthalene have been synthesized and their absolute configurations assigned using the exciton chirality c.d. method.

THE principal initial step in the metabolism of polycyclic aromatic hydrocarbons (PAHs) by mammals is the formation of their monoepoxide derivatives which are further transformed into numerous metabolites such as *trans*- dihydrodiols (epoxide hydrase) and phenols (thermal isomerisation via the NIH shift).¹ A recent study² on the metabolism of naphthalene in rats presented evidence indicating the *in vivo* intermediacy of *anti*-naphthalene 1,2:3,4-dioxide. This pathway was further implicated as a possible novel mode of metabolism of other PAHs.² In conjunction with our stereochemical and biological studies of the metabolites of PAHs, we have synthesized optically active *anti*-benzene and *anti*-naphthalene 1,2:3,4-dioxides^{3,4} and determined their absolute configurations.



 TABLE.
 Physical properties of optically active anti-benzene and anti-naphthalene 1,2:3,4-dioxides.^a

	(1)	(2)
M.p./°C	5354 ^b	132—134°
$[\alpha]_{\rm D}^{25}/^{\circ}$	+170.3	+119.7
	$(c \ 0.301, \text{CHCl}_3)$	$(c \ 0 \ 112, \ CHCl_{3})$
C.d. (cyclohexane-	$\Delta \epsilon_{222} + 2.14$	$\Delta \epsilon_{275} + 0.120$ $\Delta \epsilon_{275} + 0.114$
(10xall 45.1)		$\Delta \epsilon_{268} + 0.112$
		$\Delta \epsilon_{268\cdot 5} + 0.090$
		$\Delta \epsilon_{257\cdot 5} + 0.088$
		$\Delta \epsilon_{228\cdot 5} + 3\cdot 11$

 $^{a}>98$ % optical purity based on the diastereometic purity of their (-)-MTPA ester precursors. b M.p. of racemic (1): 58—59 °C (ref. 3c). $^{\circ}$ M.p. of racemic (2): 99—100 °C (ref. 4).

The racemic all-trans diol dibromide (3), prepared from *p*-benzoquinone in 68% overall yield,^{3c} was readily resolved via its bis-(-)- α -methoxy- α -trifluoromethylphenylacetyl [(-)-MTPA] esters⁵ (4) (81%). Two fractional recrystallisations of the diastereomers (4) from ether-benzenehexanes (5:1:1) provided the less polar isomer (4a), m.p. 140—142 °C, $[\alpha]_D^{25}$ + 11.7° (c 1.011, CHCl_3), and the more polar isomer (4b), m.p. 178—180 °C, $[\alpha]_D^{25} - 59.9^\circ$ (c 1.008, CHCl₃), in 48 and 41% recovery, respectively. Each isomer was shown to be over 98% diastereomerically pure from its 360 MHz ¹H n.m.r. spectrum. The less polar ester (4a) was then hydrolysed with NaOMe in MeOH-Et₂O at 0 $^{\circ}\mathrm{C}$ for 3 h to give the monoepoxide (5), m.p. 101-102 °C, $[\alpha]_{D}^{25} + 170.6^{\circ}$ (c 0.812, CHCl₃), in 80% yield. Further treatment of the monoepoxide (5) with KOH-MgSO₄ in anhydrous ether gave (+)-anti-benzene 1,2:3,4-dioxide (1) (Table) in 92% yield. † Use of the same sequence of reactions on (4b) provided (-)-anti-benzene 1,2:3,4-dioxide, $[\alpha]_{\rm D}^{25}$ -170.0 °(c 0.821, CHCl_a).

The stereochemistry of the dioxide was assigned using the exciton chirality c.d. method.⁶[‡] Namely, the *trans*-diol (6), m.p. 86—87 °C, $[\alpha]_D^{25} + 43.9^\circ$ (c 0.598, MeOH), obtained from the dioxide (1) using LiAlH₄ (72% yield), was converted into the bis-*p*-chlorobenzoate (7), m.p. 121—123 °C, $[\alpha]_D^{25} + 191.5^\circ$ (c 0.273, CHCl₃). The c.d. spectrum of the dibenzoate (7) showed a typical set of Cotton effects $[\Delta\epsilon_{247.5} + 32.7, \Delta\epsilon_{236.5} 0, \text{ and } \Delta\epsilon_{231} - 8.6$ in MeOH-dioxan (9:1)] ascribable to the positive chirality of the two benzoyloxy-groups in (7), thus assigning the 1*S*,2*S*,3*S*,4*S*-stereochemistry to the dioxide (1).



 $MTPA = \alpha$ -methoxy- α -trifluoromethylphenylacetyl

Resolution of anti-dioxides of naphthalene and their stereochemical assignments were carried out in a similar fashion. The racemic all-trans diol dibromide (8), m.p. 186 °C, was synthesised from 1,4-naphthoquinone in 64%overall yield through a modification of the method used for the synthesis of (3).^{3c} Thus, treatment of 1,4-naphthoquinone with excess of bromine in Et₂O yielded an extremely labile trans-2,3-dibromide which was immediately reduced with LiAlH₄ in tetrahydrofuran (THF), giving the desired all-trans-diol dibromide (8).§ The less polar (-)-MTPA ester (9a) [43% recovery from (9), > 98% diastereometric purity], m.p. 185–187 °C, $[\alpha]_D^{25}$ + 14.0° (c 1.512, CHCl₃), was obtained by three fractional recrystallisations of the bis-(-)-MTPA esters (9) [83% from (8)] from Et₂O-CHCl₃ (1:1). The diastereomer (9a) was converted into (+)-antinaphthalene 1,2:3,4-dioxide (2) (Table) in 62% yield using NaOMe in MeOH-Et₂O (room temperature, 6 h). The more polar isomer (9b) [obtained by fractional recrystallisations as above in 39% yield from (9), > 98% diastereometic purity], m.p. 137–139 °C, $[\alpha]_D^{25} - 21.3^\circ$ (c 1.213, CHCl₃), was similarly converted into (-)-anti-naphthalene 1,2:3,4dioxide, $[\alpha]_{\rm D}^{25}$ - 120.3° (c 0.560, CHCl₃). The stereochemistry was assigned based on the c.d. spectrum of the bis-*p*-chlorobenzoate (11), m.p. 171–173 °C, $[\alpha]_{D}^{25}$ + 174.8° (c 0.253, CHCl₃), of the trans-2,3-diol (10), m.p. 110-112 °C, $[\alpha]_{D}^{25} + 35.0^{\circ}$ (c 0.422, CHCl₃). The trans-2,3-diol (10) was obtained via LiAlH₄ treatment of the dioxide (2) (79 % yield).

 \dagger Attempts to obtain the dioxide (1) directly from the (-)-MTPA ester (4a) under a variety of conditions were unsuccessful, invariably providing only a low yield of the dioxide (1) and a substantial amount of its degradation products.

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[‡] Although some discussion of the basis of the exciton c.d. method has been stimulated by the incorrect assignment of the electric transition dipole (see J. Tanaka, C. Katayama, F. Ogura, H. Tatemitsu, and N. Nakagawa, J. Chem. Soc., Chem. Commun., 1973, 21; for the correct assignment see: S. F. Mason, *ibid.*, 1973, 239), the present examples are believed to be unambiguous because of the use of the chromophore whose electric transition dipole has been well established (ref. 6).

[§] Treatment of (8) with NaOMe in MeOH- Et_2O at room temperature for 4 h provided racemic *anti*-naphthalene 1,2:3,4-dioxide in 88% yield. This procedure, when applied to the synthesis of racemic *anti*-naphthalene dioxide, is superior, in yield and cleanness of the reaction, to the known methods (ref. 4).

The positive chirality of the two benzoyloxy-groups in (11), determined from its c.d. spectrum in MeOH-dioxan (9:1) $(\Delta \epsilon_{248} + 25.9, \Delta \epsilon_{238.5}, 0, \text{ and } \Delta \epsilon_{232} - 12.7)$, proved the 1S, 2S, 3S, 4S-stereochemistry for the (+)-dioxide (2).

The method described above for the synthesis of highly optically active dioxides and the determination of their absolute configuration may be applied to other anti-dioxides of PAHs. Preliminary studies indicate that all racemic and optically active dioxides of benzene and naphthalene are mutagenic in the Ames test; the benzene dioxides, though somewhat less active than the well known mutagen ethyl methanesulphonate, showed significantly stronger activity than the naphthalene analogues.⁷

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