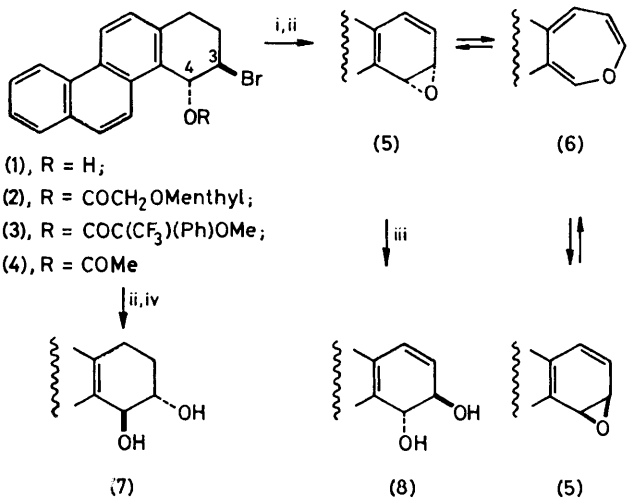
Thermal Racemization of a Chiral Arene Oxide Metabolite: Chrysene 3,4-Oxide

By DEREK R. BOYD,* MICHAEL G. BURNETT, and RUTH M. E. GREENE
(*Department of Chemistry, The Queen's University of Belfast, Belfast* BT9 5AG, *N. Ireland*)

Summary Chrysene 3,4-oxide, a major initial mammalian metabolite of chrysene, now synthesised in optically active form and configurationally assigned, has been found to racemize thermally with an activation energy of 25·2 kcal mol^{-1}, consistent with an earlier perturbational molecular orbital calculation-predicted oxepin intermediate mechanism.

CHIRAL arene oxides of polycyclic aromatic hydrocarbons (PAHs) all contain a common 6π-electron system which may, in principle, racemize through a thermally allowed disrotatory ring-opening process *via* an oxepin intermediate. The recent development of a general synthetic route to chiral arene oxides[1,2] has now made a study of their racemization possible. Few previous racemization studies on chiral epoxides have been reported since the rates are generally slow. Thus in one study[3] the reaction has been shown to occur at *ca.* 470 K *via* a conrotatory electrocyclic ring opening of the 4π oxiran ring. The arene oxides of monocyclic aromatic compounds (and some PAHs[4]) on the other hand racemize too rapidly to allow them to be studied. In such cases the arene oxide ring can open by an allowed electrocyclic process to form an unstable achiral oxepin intermediate (racemization).

This mechanism is supported by perturbational molecular orbital (PMO) calculations[4,5] which also provide a theoretical estimate of the relative configurational stabilities for a series of PAH arene oxides. This calculated order agrees with experimental results for naphthalene,[1] anthracene,[1] and phenanthrene,[4] and the predicted configurational stabilities for the three arene oxides in the benz[*a*]anthracene series studied to date[6] have subsequently been confirmed experimentally. The synthesis of chrysene 3,4-oxide (**5**) has been undertaken since the PMO results[4,5] suggested that the racemization rate should be measurable at ambient temperature. This prediction has also been confirmed and the first measurement of the racemization barrier for a chiral arene oxide has been made.



SCHEME. *Reagents:* i, *N*-bromosuccinimide; ii, NaOMe–tetrahydrofuran (THF); iii, H_2O–epoxide hydrolase; iv, H_2O–THF (pH 3).

The synthetic route used for chrysene 3,4-oxide (**5**) (the biosynthetic precursor of the most abundant dihydrodiol isolated from mammalian metabolism products of chrysene[7,8]) is similar to that used previously[1,2,6] for chiral arene oxides and is based upon a chromatographic separation of the diastereoisomeric esters (**2**) of the bromohydrin (**1**) and subsequent conversion of the bromo-ester (**4**) into the desired arene oxide (**5**). A significant improvement in this general method was achieved by the use of the methoxy-

(trifluoromethyl)phenylacetyl (MTPA) derivatives (**3**). The latter bromo-esters were more easily separated chromatographically and could be converted into the final arene oxide in two steps (i, ii) (Scheme). Using similar methods to those previously reported[1,2,6] (chromatographic characteristics and n.m.r. methods) the absolute configurations were determined (Table 1) and are in agreement with a recent independent stereochemical assignment for the diols (**7**) and (**8**).[8]

TABLE 1. Optical rotation and absolute stereochemistry of chiral structures (**1**)—(**5**), and (**7**)—(**8**).

Compound	$[\alpha]_D^a$/°($CDCl_3$)	Absolute stereochemistry
(**1**)	−21	(3*R*, 4*R*)
(**2**)	−83[a-c]	(3*R*, 4*R*)
(**3**)	+14[d,e]	(3*R*, 4*R*)
(**4**)	−169	(3*R*, 4*R*)
(**5**)	+224	(3*S*, 4*R*)
(**7**)	+23[f]	(3*S*, 4*S*)
(**8**)	−313[f,g]	(3*R*, 4*R*)

[a] Minimal value on crude oil. [b] From (−)-menthoxyacetic acid. [c] Less polar diastereoisomer; more polar form $[\alpha]_D$ + 37° (minimal value on crude oil). [d] From (−)-methoxy(trifluoromethyl)phenylacetic acid. [e] Less polar diastereoisomer; more polar form $[\alpha]_D$ − 1°. [f] THF solution. [g] Ref. 7.

The optically active sample of chrysene 3,4-oxide (**5**) showed a large $[\alpha]_D$ value (+224°) analogous to those found for comparable arene oxides of PAHs[1,2,6] but it was not considered to be the maximum possible value since a small degree of spontaneous racemization at ambient temperature unavoidably occurred both during and after the work-up procedure. Kinetic studies on samples of (**5**), purified by rapid recrystallization, were carried out polarimetrically.†

The absence of decomposition during the kinetic studies was determined by n.m.r. analysis. The racemization process followed first-order kinetics over a range of temperatures (292—322 K) in $CDCl_3$ solution (containing a trace of Et_3N to prevent acid-catalysed decomposition). A range of activation parameters was obtained from the rate constants (Table 2) which are in accord with a racemization mechanism

TABLE 2. Activation parameters for the thermal racemization of (**5**).[a]

T/K	$k \times 10^6$/s^{-1}	$\Delta G^{\ddagger}$/kcal mol^{-1}
292·2	3·51	24·35
297·7	7·99	24·34
308·3	35·6	24·32
317·9	120	24·32
321·7	186	24·34

E_a 25·15±0·19 kcal mol^{-1}. $\log_{10} A$ 13·394±0·1.
$\Delta H^{\ddagger}$ 24·55±0·02 kcal mol^{-1}. $\Delta S^{\ddagger} = 0{\cdot}699 \pm 0{\cdot}001$ cal mol^{-1} K^{-1}.

[a] The statistical errors are misleading since the constants were obtained from a specially purified sample of one enantiomer which partially racemized at each stated temperature from 292·2 K until total racemization was observed at 321·7 K. Detailed reproducibility tests are incomplete but the upper limits of error suggested are: $\Delta S^{\ddagger}$±1·2 cal mol^{-1} K^{-1}, $\Delta H^{\ddagger}$±0·4 kcal mol^{-1}, and $\Delta G^{\ddagger}$±0·2 kcal mol^{-1}.

proceeding *via* the oxepin intermediate (**6**). The E_a value of 25·2 kcal mol^{-1}‡ obtained in the present study is the first reported measurement of a barrier to racemization of a chiral arene oxide and is much lower than those previously reported for the racemization of 'normal' epoxides (E_a 41·1 and 35·9 kcal mol^{-1} for *cis*- and *trans*-2-phenyl-3-*p*-tolyloxiran, respectively[7]).§ The low value of $\Delta S^{\ddagger}$ for the racemization of the arene oxide (**5**) (0·7 cal mol^{-1} K^{-1}) is comparable to those found in the epoxide racemization study (−3 to −6 cal mol^{-1} K^{-1})[7] and is again consistent with the transition state being similar to the oxepin (**6**) which involves a relatively small degree of ordering between (**5**) and (**6**).

Mammalian metabolism of chrysene showed a marked preference (> 95%) for the formation of the (−)-(3*R*, 4*R*)-3,4-dihydrodiol metabolite (**8**)[7,8] and it is probable that it was derived exclusively from rapid enzyme-catalysed hydration of the intermediate arene oxide (**5**) having (+)-(3*S*, 4*R*) stereochemistry.

(*Received, 5th May* 1981; *Com.* 531.)

† A thermostatically controlled polarimeter cell (±0·1 K) was used in conjunction with a Perkin-Elmer 241 automatic polarimeter ($CDCl_3$, 546 nm) and chart recorder.

‡ 1 cal = 4·184 J.

§ Further kinetic studies on crude samples of compound (**5**) derived from the mother liquors after recrystallization showed slight evidence of decomposition but also yielded $\Delta G^{\ddagger}$ values within 0·2 kcal mol^{-1} of those in Table 2.

[1] M. N. Akhtar, D. R. Boyd, and J. G. Hamilton, *J. Chem. Soc., Perkin Trans.* 1, 1979, 2437.
[2] D. R. Boyd, G. S. Gadaginamath, A. Kher, J. F. Malone, H. Yagi, and D. M. Jerina, *J. Chem. Soc., Perkin Trans.* 1, 1980, 2112.
[3] H. H. J. MacDonald and R. J. Crawford, *Can. J. Chem.*, 1972, **50**, 428.
[4] D. R. Boyd, J. D. Neill, and M. E. Stubbs, *J. Chem. Soc., Chem. Commun.*, 1977, 873.
[5] D. R. Boyd and M. E. Stubbs, manuscript in preparation.
[6] D. R. Boyd, K. A. Dawson, G. S. Gadaginamath, J. G. Hamilton, J. F. Malone, and N. D. Sharma, *J. Chem. Soc., Perkin Trans.* 1, 1981, 94; D. R. Boyd, G. S. Gadaginamath, N. D. Sharma, A. F. Drake, S. F. Mason, and D. M. Jerina, *ibid.*, 1981, 2233.
[7] K. P. Vyas, H. Yagi, W. Levin, A. H. Conney, and D. M. Jerina, *Biochem. Biophys. Res. Commun.*, 1981, **98**, 961; *errata, ibid.*, in the press.
[8] M. Nordqvist, D. R. Thakker, K. P. Vyas, H. Yagi, W. Levin, D. E. Ryan, P. E. Thomas, A. H. Conney, and D. M. Jerina, *Mol. Pharmacol.*, 1981, **19**, 168.