Verification of Stereospecific Dyotropic Racemisation of Enantiopure *d* and *l*-1,2-Dibromo-1,2-diphenylethane in Non-polar Media†

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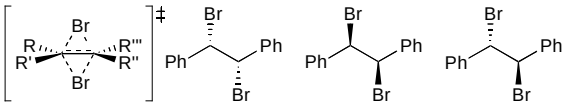
Publication data **[DO NOT ALTER/DELETE THIS TEXT]**
DOI: 10.1039/b000000x [DO NOT ALTER/DELETE THIS TEXT]

The first example of a dyotropic rearrangement of an enantiomerically pure, conformationally unconstrained, vicinal dibromide confirms theoretical predictions: *d* and *l*-1,2-dibromo-1,2-diphenylethane racemise stereospecifically in refluxing benzene without crossover to the *meso*-isomer. An orbital analysis of this six-electron pericyclic process is presented.

In 1952 Grob and Winstein[1] elucidated the mechanism of the long-known mutarotation of 5α,6β-dibromocholestane (the bromination product of cholest-5-ene).[2] Remarkably, they concluded that the two bromines migrate simultaneously and intramolecularly via an intermediate or TS[3] (typically represented by **A**) with essentially equivalent Br's having very little charge separation. Reetz[4] named, classified, and defined such "dyotropic" rearrangements[5] as uncatalysed[6] pericyclic processes in which two sigma bonds interchange under orbital symmetry control: dyotropic rearrangements involving the stereospecific exchange of two migrating groups in 1,2-anti conformations necessarily lead to inversion of configuration at both positions.[3-5] The observation of rearrangements of substituted 1,2-dibromocyclohexanes and other alkyl dibromides[7] as well as several computational studies[8-10] support the generality of such vicinal dihalide reactions. However, there has been no direct experimental verification of a concerted *dyotropic* rearrangement of an acyclic 1,2-dibromide. Such dyotropic rearrangements of symmetrical dibromides having *dl* and *meso* isomers should result in the smooth racemization of the *d*- or *l*-dibromide enantiomers by inversion of configuration at each of the stereocentres, without any interconversion into the *meso* isomer.‡ Such a stereochemical outcome would be a signature for a dyotropic mechanism and amenable to experimental study. The only report of a simple, optically active, 1,2-dibromide in which both stereogenic centres bear bromine atoms indicated that chiral 2,3-dibromobutane had not racemized after nine years![§] This corresponds to a 29 kcal mol^{-1} lower limit for the free energy of a dyotropic rearrangement. The present study seeks to demonstrate such rearrangements by employing computational searches to identify promising candidates and conditions for experimental verification. We show herein that computations predict that the dyotropic rearrangement of *d* or *l*-1,2-dibromo-1,2-diphenylethane (stilbene dibromide, **1**) in solvents of low polarity is favoured over alternative ionic interconversion mechanisms,[11] and demonstrate experimentally that enantiomerically enriched *d* and *l*-**1** undergo smooth interconversion (*i.e.* racemisation) via dyotropic rearrangement in benzene solution at reflux with no crossover to the meso-diastereoisomer (**2**). We also present an orbital analysis for this six-electron pericyclic process.



A (+)-(*S*,*S*)-**1** (-)-(*R*,*R*)-**1** **2**

The first objective, to locate a simple dibromide more reactive than 2,3-dibromobutane toward dyotropic rearrangement, was met when our computations predicted that *dl*-1,2-dibromo-1,2-diphenylethane (**1**) had a sufficiently low free energy barrier to faciliate experimental study. The available theoretical data on dyotropic barriers[8-10] had not included this compound.¶

Isomerisation of **1** and its *meso* isomer **2** via ion-pair or other polar mechanisms may also be expected, at least in ionising solvents where benzyl cation-type stabilisation favor ionic processes.[11] Indeed, the related bromination of *trans*- and *cis*-stilbenes and the debromination and other reactions of the corresponding *meso*- and *dl*-dibromides in such solvents are reported to be complex and to depend on the conditions.[11] Although the possibility has not been considered in the literature, we wondered if our predicted exchange in low dielectric media of two bromine atoms of the *d*- or *l*-**1** enantiomer through non-polar dyotropic transition states (**A**) would actually be favoured.

The computed[¥,12,13] transition structures for dyotropic rearrangement lack ion-pair character, having modest dipole moments (~4.6 D for **1**) and are little affected (~1-2 kcalmol^{-1}) by low polarity solvents such as benzene (Table 1). Methyl or alkyl substituents lower the barriers modestly (entries 1-3); the computed barrier for the dissymmetric system with two phenyl groups (entry 4) is low enough for experimental verification. The computed intrinsic reaction coordinate, as well as the transition structure, reactant, and product geometries for the dyotropic *dl*-1,2-dibromo-1,2-diphenylethane (**1**) rearrangement are depicted in Figure 1. Dyotropic shifts of the bromines result in direct interconversion (*i.e.* racemization) of the *d*- or *l*-enantiomer without any intervention of the *meso* isomer.

† Electronic Supplementary Information (ESI) available: General experimental, experimental details and characterising data for bromides **1** and **2**, ^{1}H and ^{13}C NMR spectra for dibromides **1** and **2**, separation of *d*- and *l*-1,2-dibromo-1,2-diphenylethane by chiral HPLC methods, experimental details for dyotropic rearrangement of *d* and *l*-**1**, HPLC analysis of dyotropic rearrangement, ^{1}H NMR spectra post-dyotropic rearrangements, kinetic analysis of dyotropic rearrangements, data for dyotropic rearrangement of *d*- and *l*-**1** in benzene at 80 ˚C and graphical extraction of rate constant for dyotropic rearrangement of *d*- and *l*-**1** in benzene at 80 ˚C.

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Table 1. Substituent effects on dyotropic isomerization barriers. [a,b]

Entry	Dibromide	Free energy barrier, $\Delta G^{\ddagger}_{353}$
1	1,2-dibromoethane	31.3
2	*dl*-2,3-dibromobutane	23.7
3	*dl*-1,2-dibromocyclohexane	25.4
4	*dl*-1,2-dibromo-1,2-diphenylethane (**1**)	21.7 (21.0)[c]
5	**1**, ion-pair mechanism	27.0 (27.8)[c]

[a] In kcal mol^{-1} computed for a benzene continuum solvent model at the B3LYP/Def-2 QZVPP level. [b]See interactivity box.[¥] [c]At the B3LYP/6-311G(d,p) –simulated benzene level.

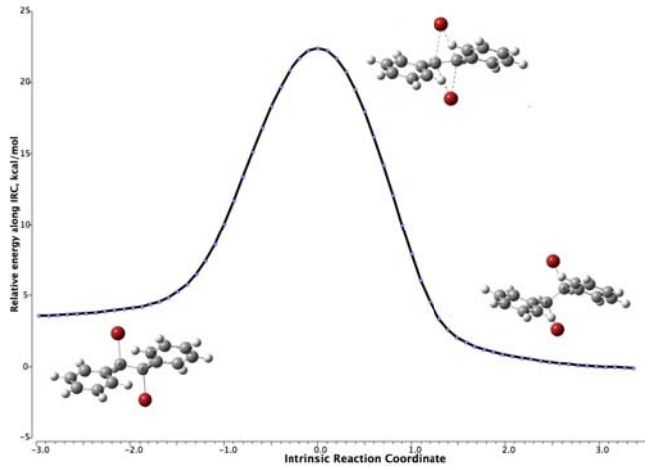

Figure 1. Intrinsic reaction coordinate (IRC) for the dyotropic interconversion of *d*/*l*-1,2-diphenyl-1,2-dibromoethane, computed at the B3LYP/6-311g(d,p) level with a continuum solvent correction for benzene. As C_2-symmetry is maintained throughout, the asymmetry of the IRC is due to the different phenyl conformations of reactant and product. These conformations can interconvert by a second dynamic process with only a small barrier. The C-C bond length is 1.437 Å at the transition state. See interactivity box for animations. [¥]

In contrast to the dyotropic mechanism (Table 1), our computations[¥] find that the lowest energy alternative transition state for **1** with ion-pair character (entry 5) has a much larger dipole moment (~13 D). The highest computed free energy barrier for this pathway (in simulated benzene) is ~ 5.3 kcalmol^{-1} above that of the dyotropic mechanism; hence, the latter is clearly favoured in such non-polar media.

Individual *dl*-1,2-dibromo-1,2-diphenylethane enantiomers (**1**) were required for the experimental study. Attempts to prepare the *d* or *l*-dibromide[14] by double Appel bromination[15] of the readily available enantiomerically pure hydrobenzoin were unsuccessful; good yields of *E* and *Z* stilbene mixtures (typically 3:1) were obtained instead. However, chiral HPLC methods[††] were able to separate *dl*-dibromide **1**[**] (obtained by bromination of *Z*-stilbene with Br_2 in dichloromethane solution)[16] into its enantiomers. Analogous bromination of *E*-stilbene gave *meso*-1,2-dibromo-1,2-diphenylethane **2**,[**] required as an authentic control sample.

Our aim was to test the theoretical predictions that racemization (by a dyotropic rearrangement) but not *dl*-*meso* interconversion should occur under favorable (*i.e.*, non-polar) conditions.[‡‡] We first explored the thermal stability of dibromides **1** and **2** in various solvents.[17] Heating either *dl*-**1** or *meso*-**2** in polar aprotic (DMF at 120 ˚C, DMSO at 80 ˚C) or in polar protic solvents (1,1,1,3,3,3-hexafluoroisopropanol at 60 ˚C) led to complex product mixtures.[§§] On the basis of earlier observations,[1,3,7,11] and our computations, we expected non-ionizing solvents to be optimal for the detection of dyotropic rearrangements and the suppression of side reactions. Indeed, in direct contrast to our results in polar media, no appreciable changes in the ^{1}H NMR spectra of either *dl*-**1** or *meso*-**2**.were observed after extended heating at reflux in either benzene solution (5 days) or in dichloromethane (3 days), in the absence of catalysts,[¶¶]

As this establishes that no *dl*-*meso* interconversion occurs in benzene solution at 80 ˚C, single *d* and *l*-dibromide enantiomers were heated separately in benzene solution at 80 ˚C to monitor any dyotropic rearrangement. Much to our delight, slow conversions of *R*,*R*-**1** into *S*,*S*-**1**, and also *S*,*S*-**1** into *R*,*R*-**1** at identical rates, were observed with typical first order kinetics (k = 0.0015 s^{-1} at 80 ˚C, equivalent to $\Delta G^{\ddagger}_{353}$ 25.3 kcal mol^{-1}),[††] and without any formation of *meso*-dibromide diastereoisomer **2**. Thus, this behavior of individual stilbene dibromide enantiomers as stereochemical probes demonstrates the first dyotropic rearrangement of enantiomerically pure, conformationally unconstrained vicinal dibromides. The absence of *meso*-isomer **2** under these conditions rules out possible alternative dissociation-recombination pathways involving an intermediate bromonium ion–bromide anion pair (as seen in solvents of high polarity), or free stilbene and molecular bromine.[11] In line with the theoretical prediction that the dyotropic transition state is stabilized by the two phenyl groups (Table 1), our observed first order rate constants are up to two orders of magnitude faster than the rate constants for the mutarotation of dibromocholestane previously determined by Grob and Winstein[1] and by Barton and Head,[3] as well as the rate measurements of Barili *et al.*[7] on sterically uncongested *trans*-1,2-dibromocyclohexanes.

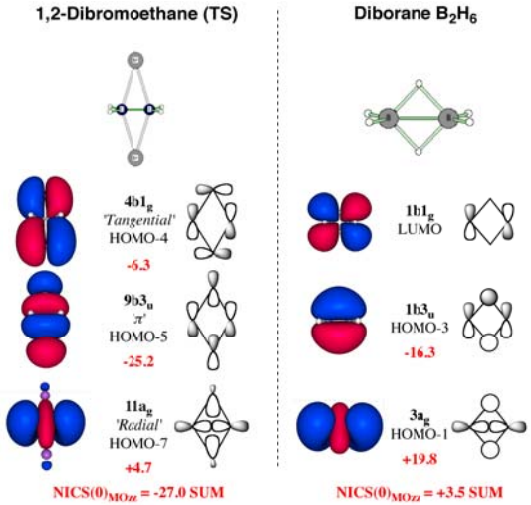

Figure 2. Orbital analysis for dyotopic rearrangement of 1,2-dibromethane showing the three molecular orbitals involved in the transition state and a comparison with the corresponding B_2H_6 MO's. The NICS(0)$_{MOzz}$ values and their sums are the out-of-plane (zz) tensor component of the isotropic NICS of each MO shown, computed at the molecule centers at PW91/6-311+G(d,p).[18] See also the interactivity box for further detail, including a curly arrow notation for the process. [¥]

The computed CC bond lengths (~1.44Å)[¥] of the dibromo dyotropic transition states suggest partial double bond character (Wiberg bond index ~1.215)[¥] and require explanation. Previous orbital analyses[4,5,10] did not address this issue directly nor clearly define the number of electrons participating in this pericyclic process. Our orbital analysis of 1,2-dibromoethane shown in Figure 2 defines this six-electron pericyclic process; three doubly occupied orbitals ($4b1_g$, $9b3_u$ and $11a_g$) comprising what can be described as tangential, π, and radial MOs, respectively, are involved. The previous analyses[5,10] did not include the radial MO. The combination of these three MOs, as well as lower MOs (see interactivity box), result in the partial double bond character. Thus, representation **A** showing partial double bond character, first used by Winstein[1] and by Barton[3], is clearly appropriate.

The strong diatropic ring current shown by the dissected $NICS(0)_{MOzz}$ sum of the three orbitals in Figure 2 (–27.0 ppm) documents the strongly aromatic character of the six-electron, dyotropic transition state. In contrast, $NICS(0)_{MOzz}$ = +3.5 ppm of the bridging B_2H_6[¥] system, involving only four electrons, is clearly not aromatic.

We thank Thais Cailleau (Imperial College London) for preliminary research on attempted Appel brominations of hydrobenzoins, and Dr. Andrew McKinley (Imperial College London) for helpful discussions. The work in Georgia was supported by NSF Grant CHE-105-7466. This paper is dedicated to the memory of Saul Winstein and Cyril A. Grob on their 100th and 95th birthdays, respectively.

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Notes and references

‡ Dyotropic rearrangement of such *meso* isomers cannot be detected since it merely involves interconversion to its *superimposable* mirror image (*i.e.*, RS <-> SR).

§ A neat sample of optically active 2,3-dibromobutane, $[\alpha]_D$ -2.43, gave a reading of $[\alpha]_D$ -2.17 after standing for nine years in a sealed ampoule (ref. 1).

¶ The dyotropic rearrangements of (1,2-dichloroethyl)benzene, and 9,10-dibromo-9,10-dihydrophenananthrene have been investigated computationally (see ref. 10), but not the effect of simple phenyl groups in the stilbene dibromides.

¥ The computations used the Gaussian 09 program (ref. 12) at the B3LYP/Def-2 QZVPP (ref. 13a) density functional level. All computed harmonic frequencies of fully optimized minima were real, whereas transition structures had a single imaginary frequency. Intrinsic reaction coordinate (IRC) analyses of the minimum energy pathways (MEPs) confirmed the connection of transition structures to the reactants and products described in the text. The polarized continuum model (CPCM) (ref. 13b,c) implemented in the Gaussian 09 program was used to simulate the bulk solvation. See the interactivity box for full details.

†† See Electronic Supporting Information for details.

** The *dl-* and *meso*-isomers can be distinguished readily by their benzylic ^{13}C NMR ($CDCl_3$) resonances at 59.2 and 56.1 ppm, respectively, by their ^1H NMR ($CDCl_3$) spectra in the aromatic region, and by their 100-102 and 240-242 ˚C melting points, respectively. The *meso* compound is much less soluble than its *dl*-isomer.

‡‡ The *dl-meso* interconversion might occur by mechanisms involving (a) elimination to free *E* or *Z* stilbene and Br_2 followed by non-stereospecific re-addition (ref. 16) or (b) free carbocations and/or (partially) bridged bromonium ions, C-C bond rotation and/or non-selective bromide return. See ref. 11 for excellent discussions.

§§ *E*-stilbene and monobromostilbene were the major constituents of the reaction mixtures using *meso*-**2** and *dl*-**1** respectively in DMSO at 80˚C. This implicates the loss of molecular bromine (*cf.* note above) from *meso*-**2** and non-selective bromination/oxidation of substrate and/or solvent, and loss of HBr and subsequent acid mediated processes for *dl*-**1** (also see ref. 17).

¶¶ A *dl*-**1** *to meso*-**2** isomerization in refluxing benzene with catalytic molecular iodine has been reported (ref. 11d).

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