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

D. Christopher Braddock,*a Debjani Roy,b Dieter Lenoir,c Edward Moore,* Henry S. Rzepa,* Judy I-Chia Wu,* and Paul von Ragué Schleyer*a,b

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 Winston1 elucidated the mechanism of the long-known mutarotation of 5x,6x-dibromocholestanate (the bromination product of cholest-5-ene).2 Remarkably, they concluded that the two bromines migrate simultaneously and intramolecularly via an intermediate or TS1 (typically represented by A) with essentially equivalent Br’s having very little charge separation. Reetz3 named, classified, and defined such “dyotropic” rearrangements as uncatalysed 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 dibromides4 as well as several computational studies5-10 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.1 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.11 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.

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 facilitate experimental study. The available theoretical data on dyotropic barriers8,10 had not included this compound.5

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 favours 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 computed5,12,13 transition structures for dyotropic rearrangement lack ion-pair character, having modest dipole moments (\(-4.6\) D for 1) and are little affected (\(-1.2\) kcal mol\(^{-1}\)) 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 (I) 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.

* c.braddock@imperial.ac.uk; schleyer@uga.edu

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Table 1. Substituent effects on dyotropic isomerization barriers.\(^ {ab}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dibromide</th>
<th>Free energy barrier, $\Delta G^\ddagger_{353}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,2-dibromoethane</td>
<td>31.3</td>
</tr>
<tr>
<td>2</td>
<td>dl-2,3-dibromobutane</td>
<td>23.7</td>
</tr>
<tr>
<td>3</td>
<td>dl-1,2-dibromocyclohexane</td>
<td>25.4</td>
</tr>
<tr>
<td>4</td>
<td>dl-1,2-dibromo-1,2-diphenylethane (1)</td>
<td>21.7 (21.0)$^\dagger$</td>
</tr>
<tr>
<td>5</td>
<td>1, ion-pair mechanism</td>
<td>27.0 (27.8)$^\ddagger$</td>
</tr>
</tbody>
</table>

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

In contrast to the dyotropic mechanism (Table 1), our computations\(^3\) 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 kcal mol$^{-1}$ 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 hydrobromazin were unsuccessful; good yields of E and Z stilbene mixtures (typically 3:1) were obtained instead. However, chiral HPLC methods\(^16\) were able to separate dl-dibromide 1$^\ddagger$ (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$^\ddagger$, \(^\ddagger\) 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.\(^3\) 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-hexafluoropropanol at 60 °C) led to complex product mixtures.\(^\ddagger\)

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 benzene solution (5 days) or in dichloromethane (3 days), in the absence of catalysts.\(^6\)

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$^{-1}$)\(^7\), 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 dibromochloestane previously determined by Grob and Winston\(^1\) and by Barton and Head,\(^3\) as well as the rate measurements of Barli et al.\(^7\) on sterically uncongested trans-1,2-dibromocyclohexanes.
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 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 (4b1g, 9b3u and 11ag) comprising what can be described as tangential, π, and radial MOs, respectively, are involved. The previous analyses 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 Winston and by Barton, is clearly appropriate.

The strong diatropic ring current shown by the dissected interactivity box, result in the partial double bond character. Thus, the bridging B2H6 dyotropic transition state. In contrast, NICS(0)MOzz = +3.5 ppm of the bridging B2H6 system, involving only four electrons, is clearly not aromatic. We thank Thais Cailleur (Imperial College London) for preliminary research on attempted Aml brominations of hydrobenzoins, and Dr. Andrew McKinley (Imperial College London) for helpful discussions. The work in Georgia was supported by NSF Grant CHE-1057466. This paper is dedicated to the memory of Saul Winston and Cyril A. Grob on their 100th and 95th birthdays, respectively.

D. Christopher Braddock, Dept. Deebani Roy,* Dieter Lenoir,† Edward Moore,‡ Henry S. Rezua, Judy L-Chia Wu,§ and Paul von Ragué Schleyer¶

‡‡  See Electronic Supporting Information for details.

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).

‡‡ The dyotropic rearrangements of (1,2-dichloroethyl)benzene, and 9,10-dibromo-9,10-dihydroanthracene 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/Def2-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 (PCM) (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 di- and meso-isomers can be distinguished readily by their benzylic 13C NMR (CDCl3) resonances at 59.2 and 56.1 ppm, respectively, by their 1H NMR (CDCl3) 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 di-meso interconversion might occur by mechanisms involving (a) elimination to free E or Z stilbene and Br2 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. 11b).