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# Steric Isotope Effects

## II.* The Deuterium Isotope Effect in the Racemization of (+)-2,2′-Dibromo-4,4′-dicarboxybiphenyl-5,5′-$d_2$

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The title compound has been synthesized and its rate of racemization compared with that of the corresponding protium compound. The kinetic isotope effect ratio, $k_D/k_H$, was found to be 1.02 ± 0.02.

Previous work[1] on the deuterium isotope effect in the racemization of (+)-2,2′-dibromo-4,4′-dicarboxybiphenyl specifically deuterated in the 6 and 6′ positions demonstrated that the presence of deuterium at the "center of reaction" increases the rate of racemization by 18 %. This was in line with what could be expected on theoretical considerations, at least qualitatively. Quantitative comparison of theory and experiment was made difficult by some uncertainty in the parameters to be used in the H···Br potential function necessary for the calculation of the (steric) isotope effect according to the theory of Bartell.[2] However, use of a potential function suggested by Howlett[3] led to quite good agreement with the experimental observations.

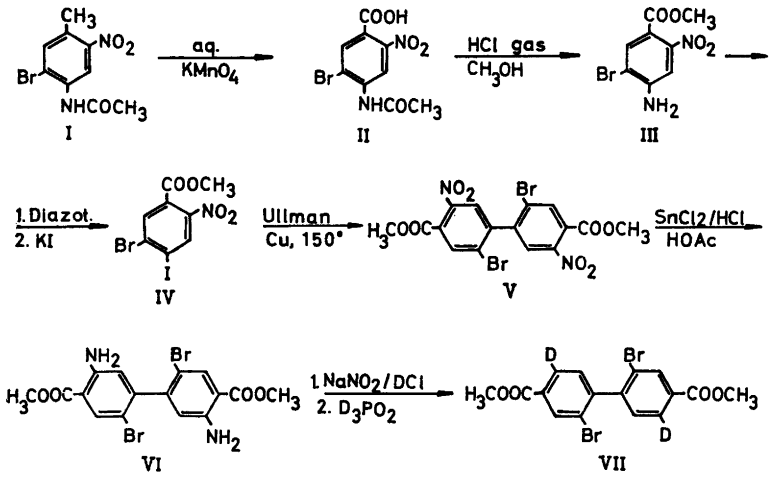
The present work was carried out in an attempt to assess the contribution, if any, of differences in inductive effect or other differences between protium and deuterium to the observed isotope effect. As discussed previously,[1] inductive differences (which could possibly affect the double-bond character of the pivot bond in the planar transition state) are not expected to be significant in this case, judging from the small magnitude of reported "inductive" isotope effects.[4] Furthermore, the absence of a noticeable influence of solvent on the isotope effect ratio was interpreted[1] as support for this assumption. In the present study, (+)-2,2′-dibromo-4,4′-dicarboxybiphenyl-5,5′-$d_2$ has been synthesized and its rate of racemization compared to that of the corresponding undeuterated compound. In this biphenyl the deuterium atoms are removed from the "center of reaction" and thus unable to influence the racemization rate by non-bonded interactions.

* Ref. 1 is considered to be Part I.

## RESULTS AND DISCUSSION

(+)-2,2′-Dibromo-4,4′-dicarboxybiphenyl-5,5′-$d_2$ was synthesized by the procedure depicted in Chart 1. Most of the steps in the synthesis have been described in detail elsewhere,[5] and thus only a brief outline will be presented here. 2-Nitro-4-acetamino-5-bromotoluene (I), prepared by acetylation of the corresponding amine,[6] was oxidized with aqueous permanganate to yield 2-nitro-4-acetamino-5-bromobenzoic acid (II), which was simultaneously hydrolyzed and esterified by the action of HCl gas in methanol to produce methyl 2-nitro-4-amino-5-bromobenzoate (III). Compound (III) was converted to the corresponding iodo derivative (IV) by diazotization followed by reaction

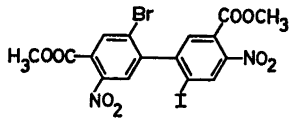
Chart 1



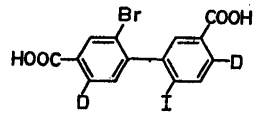

with aqueous potassium iodide. Ullmann coupling of (IV) led to 2,2′-dibromo-4,4′-dicarbomethoxy-5,5′-dinitrobiphenyl (V), which was reduced to the diaminobiphenyl (VI) by the action of a reducing agent prepared by dissolving stannous chloride in glacial acetic acid with the aid of HCl gas.[7] Introduction of deuterium was accomplished *via* reduction of the tetrazotized diamine with $D_3PO_2$ in a manner similar to that previously described[1] for the synthesis of the 6,6′-$d_2$ isomer. Two simple procedural modifications considerably facilitated this step: (i) DCl was generated *in situ* from acetyl chloride and $D_2O$; and (ii) $Cu_2O$ was used to catalyze the reduction with $D_3PO_2$. The hydrolysis of the diester (VII) with potassium hydroxide in 95 % ethanol and the secondary asymmetric transformation of the racemic acid by brucine were performed as described by Harris and Mitchell[8] for the unlabelled compound.

Despite repeated attempts at purification, the final product contained a few percent of a tenacious optically active impurity with high specific rotation, which led to curved first-order kinetic plots (*vide infra*). Treatment with activated charcoal, sublimation, thin-layer chromatography of the methyl

ester on silica using six different solvent combinations, and column chromatography of the methyl ester on alumina were among the unsuccessful procedures employed in attempting to remove the impurity. This difficulty of separation was indicative of structural similarity between the impurity and the main product. The only stage in the synthesis at which a second dicarboxydihalobiphenyl could be produced is of course the Ullmann coupling step. An asymmetric coupling involving the bromine atom on one molecule of (IV) and the iodine atom on another would lead to compound (VIII), which would give




VIII




IX

(IX) as the impurity in the final product. An iodine analysis * by the method of Schöniger [9] indicated the presence of 1.19 and 1.13 % iodine in two separate determinations. This corresponds to about 4 mole % of compound (IX).

A comparison of the mass spectrum ** of the deuterated product with that of the pure undeuterated material supports the above line of reasoning. The typical triplet structure of the parent peak for dibromo compounds due to the three possible combinations of $^{79}Br$ and $^{81}Br$, along with satellites from $^{13}C$ in natural abundance, was centered as expected at *m/e* 400 and 402 for the protium and deuterium compounds, respectively. The parent peak for the impurity in the spectrum of the deuterated substance occurs as a doublet centered at *m/e* 449, the molecular weight of compound (IX). An evaluation of the amount of impurity by simple peak height comparison leads to a value of 2.0 %.***

The mass spectrum showed the deuterated product to be a mixture of $d_0$, $d_1$, $d_2$, $d_3$, and $d_4$ compounds. Molecules containing more than two deuterium atoms probably arise from exchange with the diamine (VI) in the diazotization step. It was difficult to accurately determine the detailed isotopic composition of the sample by peak height measurements due to the triplet nature of the parent peak and contributions from impurity fragment ions to the height of other more suitable peaks such as $M^+-2Br$. The mass spectrum indicates that about 85 % of the molecules contain at least two deuterium atoms, and that about 92 % contain at least one. The NMR spectrum of the diester (VII) shows the near absence of peaks attributable to the 5,5′-protons, and thus it seems safe to assume that most of the deuterium-containing molecules are substituted in the 5 and/or 5′ positions.

The kinetics of the racemization in ethanol solution at $-5.7_5 \pm 0.0_8$°C were determined on a Perkin-Elmer 141 automatic reading polarimeter as

* Kindly performed by Mrs. B. Ulin at AB Hässle, Göteborg.

** Run at the Laboratory for Mass Spectrometry, Karolinska Institutet, Stockholm.

*** This mass spectrum also contains a triplet peak of unknown origin centered at *m/e* 435, about one-fourth the size of the doublet peak at *m/e* 449.

described previously,[1] using the mercury line at 436 nm. Concentrations ranged from 20.7 to 25.3 mg/ml solvent; the rate constant shows no concentration dependence in this range.[1] The protium compound gave excellent first-order plots, and the racemization rates were obtained from a least-squares treatment of the data using the Datasaab D21 computer at the Department of Medical Biochemistry of the University of Göteborg. The deuterium compound, as discussed above, gave curved plots due to the presence of an optically active impurity that racemized at about a tenth of the rate of the main component. Quite good straight-line plots could, however, be obtained by means of the following straightforward correction procedure. After an initial series of points had been taken, the racemization was allowed to proceed under the same conditions until the optical rotation of the main deuterium compound could be safely assumed to be less than 0.001°. At this point, a new series of measurements was taken, which was fitted to a straight line by a least-squares treatment. Extrapolation of this line to the time of the initial curved plot and subtraction of the extrapolated values from the original points led to a new set of data for the 5,5′-$d_2$ compound which gave an excellent least-squares fit to a straight line with a standard deviation of the same order of magnitude as that obtained with the protium compound. Data taken from a kinetic run with the deuterium compound along with the calculated correction for each point are presented in Table 1.

The absence of residual rotation was confirmed after each run by maintaining the solution at room temperature for several hours and then determining the optical rotation. In no case was the rotation thus measured outside the experimental error of $\pm$ 0.002°.

Due to the limited amount of deuterated material available after numerous purification attempts, only two kinetic runs were carried out with this substance. The reproducibility of the polarimetric method was shown to be satisfactory by seven runs on the protium compound, which gave a maximum

*Table 1.* Data from a kinetic run with 2,2′-dibromo-4,4′-dicarboxybiphenyl-5,5′-$d_2$ to illustrate the correction for the presence of a co-racemizing impurity (see text). The data were selected from among the 28 points originally taken.

| Time, sec | Observed rotation, deg. | Correction,[a] deg. | Corrected rotation, deg. |
|---|---|---|---|
| 240 | 1.774 | −0.143 | 1.631 |
| 600 | 1.542 | −0.140 | 1.402 |
| 1200 | 1.235 | −0.136 | 1.099 |
| 1830 | 0.981 | −0.133 | 0.848 |
| 2520 | 0.768 | −0.128 | 0.640 |
| 3000 | 0.649 | −0.126 | 0.523 |
| 3600 | 0.532 | −0.123 | 0.409 |
| 4830 | 0.365 | −0.116 | 0.249 |
| 6600 | 0.228 | −0.107 | 0.121 |
| 8400 | 0.156 | −0.099 | 0.057 |

[a] Calculated from the least-squares equation for the plot of $\log_e$ (rotation) *vs.* time for the impurity: $\log_e \varphi_t = -4.46 \times 10^{-5} t - 1.937$.

*Table 2.* Kinetic data on the racemization of 2,2′-dibromo-4,4′-dicarboxybiphenyl and its 5,5′-dideuterio derivative in ethanol solution at $-5.7_8 \pm 0.0_8$°C.

| Isotope | Conc. mg/ml | $10^5k$,[a] $sec^{-1}$ | Std. deviation [a] $\times 10^5$ $sec^{-1}$ | Average and max. dev. $\times 10^5$ $sec^{-1}$ |
|---|---|---|---|---|
| H | 21.9 | 40.04 | 0.07 | |
| H | 21.7 | 39.89 | 0.05 | |
| H | 21.4 | 40.72 | 0.02 | |
| H | 24.3 | 40.55 | 0.03 | |
| H | 20.7 | 40.13 | 0.03 | |
| H | 20.7 | 40.76 | 0.04 | |
| H | 25.4 | 40.35 | 0.02 | |
| | | | | 40.35 ± 0.46 |
| D | 22.1 | 40.98 | 0.04 | |
| | | 4.46 [b] | 0.12 [b] | |
| D | 25.3 | 41.30 | 0.05 | |
| | | 3.86 [b] | 0.08 [b] | |
| | | | | 41.14 ± 0.16 |

[a] From a least-squares fit of the polarimetric data.
[b] Value for correction line; see text.

deviation of about 1 % of the average rate constant. All of the kinetic data are collected in Table 2.

The kinetic isotope effect ratio, $k_D/k_H$, may be calculated from the data in Table 2 (without attempting to correct for the isotopic composition) to be $1.02 \pm 0.02$. This indicates that, as expected, inductive differences between protium and deuterium are probably not significant in determining the magnitude of the isotope effect ratio observed in the racemization of 2,2′-dibromo-4,4′-dicarboxybiphenyl and its 6,6′-dideuterio derivative.[1] It was not possible to place the deuterium atoms closer than three bonds from the "center of reaction" in the present study, but as this is only one bond further away than in the 6,6′-$d_2$ isomer, the classical attenuation of an inductive effect with distance is not expected to affect the validity of the above conclusion. This is supported by the observation of Streitwieser and Klein [10] that the deuterium isotope effect on the solvolysis of benzhydryl chloride in aqueous acetone is 1.9 % per D from the *ortho* positions and decreases to 1.5 % per D from the *meta* positions.

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