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The Deuterium Isotope Effect in the Racemization of 2,2′-Dibromo-4,4′-Dicarboxybiphenyl *

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2,2′-Dibromo-4,4′-dicarboxybiphenyl-6,6′-d_2 has been synthesized and its rate of racemization compared to that of the protium compound within the temperature interval −20 to 0°C. The rate ratio k_D/k_H was found to be about 1.18, corresponding to a $\Delta\Delta F^{\ddagger}$ value of about 90 cal/mole. The accuracy has not allowed a separation of the latter magnitude into its enthalpy and entropy components.

A computation according to Bartell, which assumes the effect to be entirely due to an internal-energy difference, gives a value of $\Delta\Delta E^{\ddagger}$ in good agreement with the experimental $\Delta\Delta F^{\ddagger}$ when a recently proposed hydrogen-bromine non-bonded repulsion potential is used. The prediction is very sensitive, however, to the choice of potential function, and the agreement might be fortuitous.

The origin of secondary kinetic isotope effects is still unclear despite extensive study in recent years. Most interpretations have been in terms of a valence-force picture of the intramolecular force field, *i.e.* these effects are usually ascribed to carbon orbital rehybridization between reactant and transition state [1] or to hyperconjugation.[2]

The importance of non-bonded interactions in molecules which are not obviously overcrowded has long been recognized in molecular spectroscopy. It is not until recently, however, that such interactions have been advanced as an explanation of secondary isotope effects. Bartell [3] has made quantitative estimates of the effects which might be expected in several relatively simple reactions. Although the order of magnitude of the predicted effects is in agreement with observations, difficulties remain in reconciling theory and experiment.[4] The main difficulties involved in computations of this kind are

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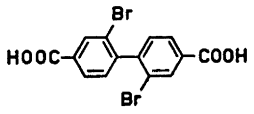
due to insufficient information about the detailed conformation of the transition state and the non-bonded potentials between different pairs of atoms.

An accurate experimental check of Bartell's computational procedure, and thus of his proposal that secondary isotope effects may be "steric" in origin, requires a reaction with a transition state of known conformation. The difference in interpenetration of the non-bonded atoms under study on going from reactant to transition state should be as large as possible in order to give rise to an easily measurable effect. For obvious reasons the reaction should follow simple kinetics and take place in a system as ideal as possible, in which medium changes due to the course of the reaction are negligible. It should also be possible to follow the reaction by means of some simple, accurate method, preferably a physical one.

The racemization of optically active biphenyl derivatives is a very attractive reaction from the experimental point of view, and steric hindrance is most often the reason that this reaction proceeds at a measurable rate. Steric effects due to hydrogen are probably an important part of the potential-energy barrier in the racemization of 9,10-dihydro-4,5-dimethylphenanthrene, studied by Mislow *et al.*[5], but the detailed conformation of the transition state is not well-known in this case, and it is thus difficult to compare the experimental results with theoretical predictions.

The situation is quite different with regard to the racemization of 2,2′-dibromo-4,4′-dicarboxybiphenyl (I): the transition state of this reaction, which



I

is believed to be planar, has been the subject of a detailed theoretical study by Westheimer and Mayer.[6,7] In this reaction, the entire potential-energy barrier is the consequence of hydrogen-bromine non-bonded interactions. It was possible to calculate the degree to which the hydrogen-bromine repulsion is released by the deformation of the bond distances and valence angles of the molecule, as well as the interatomic distance at which the hydrogen-bromine interpenetration ceases. This information affords the necessary input-data for a calculation according to the equations of Bartell.[3] The validity of the results for the transition state can be tested by means of the activation energy, which was the orginal object of Westheimer's calculations.[7] The greatest source of uncertainty is probably the repulsion potential. Since the publication of the original computations,[7] there has been some improvement in this field, and Howlett [8] has recently made a recalculation with a more reliable potential function and some other refinements. The activation energy calculated by Westheimer [7] (18 kcal/mole) and that by Howlett [8] (21.9 kcal/mole) are both in agreement with the experimentally determined values of 18.5 kcal/mole [9] and 17.4 kcal/mole (present study; see Table 4). Howlett's data lead to a prediction of the isotope effect which is in much better agreement with the experimental value than the prediction based on the work of Westheimer (*vide infra*).

The difference between the two experimental values for the activation energy is somewhat outside the combined limits of error. The reason for this discrepancy is not obvious.

PREDICTION OF ISOTOPE EFFECT

The preferred conformation of 2,2′-dihalobiphenyls is apparently that in which the two halogen atoms are in van der Waals contact.[10,11] Accordingly, it is plausible to assume that all steric interactions affecting the kinetic isotope effect arise from crowding in the transition state, *i.e.* initial-state steric effects are unaffected by deuterium substitution in the 6 and 6′ positions.

According to eqn. 5 in Bartell's paper,[3] the non-bonded interaction between two atoms may be approximately written as follows:

$$\overline{V}(r_g) \approx V(r_g) + \tfrac{1}{2}l_t^2 V''(r_g) + \tfrac{1}{8}l_t^4 V^{IV}(r_g) + \ldots . \quad (1)$$

In this expression, $V(r)$ is the potential function for the non-bonded interaction, r is the corresponding interatomic distance and r_g its mean value, which is the same for all isotopes in the first approximation. The symbol l_t^2 denotes the mean-square amplitude of vibration of the pair of atoms concerned. Bartell subdivides this quantity into a component l_m^2 that represents the zero-point motion of the hydrogen relative to the neighboring carbon and is sensitive to the isotopic hydrogen mass, and a component l_s^2 that represents the remaining part of the skeletal vibrations and is not mass-sensitive:

$$l_t^2 = l_m^2 + l_s^2 \quad (2)$$

The quantity l_m is about 17 % larger for protium than for deuterium.

If the difference in interaction between a protium and a bromine atom on the one hand and between a deuterium and a bromine atom on the other is considered, and terms arising from derivatives of V higher than the fourth are neglected, the following approximate expression is valid:

$$(\overline{V}(r_g))_H - (\overline{V}(r_g))_D \approx 0.13_5 l^2_{m(H)}[V''(r_g) + \tfrac{1}{2}l^2_{t(H)} V^{IV}(r_g)] \quad (3)$$

In the present case this difference also represents one half of the isotopic difference in activation energy, $\Delta\Delta E^{\ddagger}$. If the number of points of contact between hydrogen and bromine is taken into account, the expression for $\Delta\Delta E^{\ddagger}$ becomes:

$$\Delta\Delta E^{\ddagger} = \Delta E^{\ddagger}_H - \Delta E^{\ddagger}_D = 2 \times 0.13_5 l^2_{m(H)}[V''(r_g) + \tfrac{1}{2}l^2_{t(H)} V^{IV}(r_g)] \quad (4)$$

The estimated values of $l_{m(H)}$ and $l_{t(H)}$ for the transition state in the racemization of 2,2′-dibromo-4,4′-dicarboxybiphenyl are 0.09 Å and 0.25 Å, respectively. The potential functions used for the computation of the transition state conformation are of the simple exponential type

$$V(r) = a \exp(-r/b) \quad (5)$$

where a and b are parameters. The values of a and b used by Westheimer [7] and by Howlett [8] are presented in Table 1 together with the equilibrium hydrogen-bromine distance (r_g) derived by each of these authors. The values of $\Delta\Delta E^{\ddagger}$ calculated from eqn. (4) are given in the last column of Table 1.

Table 1. Potential parameters, equilibrium distances and isotopic differences in activation energy from data of Westheimer [7] and Howlett.[8]

Source of data	a, erg/molecule	b, Å	r_g, Å	$\Delta\Delta E^{\ddagger}$ cal/mole[a]
Westheimer [7]	2.45×10^{-7}	0.165	2.31	506
Howlett [8]	1.44×10^{-10}	0.4379	2.46	100

[a] Calculated according to eqn. (4); see text.

The repulsion potentials used by Westheimer [7] and by Howlett [8] are quite different and so are the predictions of the isotopic difference in the activation energy. Since the parameter b is small in the Westheimer potential, the expansion converges slowly and, in fact, the term containing the fourth derivative is slightly larger than the preceding one. Consequently, the full first-order $\Delta\Delta E^{\ddagger}$ value may be considerably larger than indicated by the abbreviated expansion formula given above. With Howlett's potential, on the other hand, the second term contributes no more than a seventh to the result. These differences also imply that the estimated value of $l_{t(H)}$ has a significant effect on the result obtained from Westheimer's potential, but much less on that from Howlett's.

EXPERIMENTAL RESULTS

2,2'-Dibromo-4,4'-dicarboxybiphenyl-6,6'-d_2 was synthesized in about 97 % isotopic purity (according to NMR) by a procedure that is described in detail in the section on Experimental Procedures. The principal steps of the synthesis are shown in Chart 1. Ullmann coupling of the methyl ester of 3-nitro-4-iodobenzoic acid(II) followed by bromination of the product according to the gene-

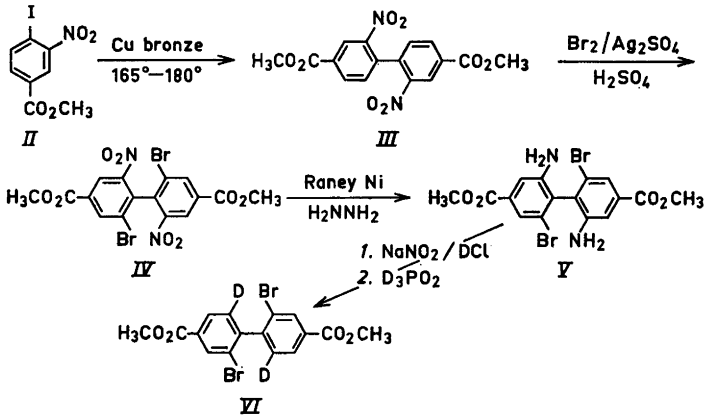


Chart I

ral method of Derbyshire and Waters[12] led to 2,2′-dibromo-4,4′-dicarbomethoxy-6,6′-dinitrobiphenyl (IV). The nitro groups were easily reduced with Raney nickel and hydrazine, and the resulting diamine (V) was further reduced (after tetrazotization) with D_3PO_2 that had been prepared by repeated exchange of H_3PO_2 with 99.8 % D_2O. The hydrolysis of the ester with potassium

Table 2. Kinetic data on the racemization of 2,2′-dibromo-4,4′-dicarboxybiphenyl and its 6,6′-dideuterio derivative in ethanol solution.

Run	Temp., °K	Isotope	$10^5\ k$, sec^{-1}	Average and max. dev. $\times\ 10^5\ sec^{-1}$	k_D/k_H	$\Delta\Delta F^{\ddagger}$, cal/mole
4	253.4	H	6.32			
7		H	6.78			
9		H	6.54			
11		H	6.32			
				6.49 ± 0.29		
14		D	7.61			
15		D	7.61			
16		D	7.99			
17		D	7.59			
				7.70 ± 0.29		
					1.19 ± 0.07	86 ± 32
18	262.9	H	23.59			
19		H	23.98			
20		H	23.58			
				23.72 ± 0.26		
21		D	27.10			
22		D	28.40			
23		D	27.79			
				27.76 ± 0.66		
					1.17 ± 0.04	82 ± 19
24	267.8	H	43.74			
25		H	44.53			
26		H	43.26			
				43.84 ± 0.69		
27		D	52.01			
28		D	51.57			
29		D	51.10			
				51.56 ± 0.46		
					1.18 ± 0.03	86 ± 13
30	273.0	H	84.26			
31		H	83.03			
32		H	82.75			
				83.35 ± 0.91		
34		D	99.03			
35		D	99.39			
36		D	96.40			
				98.27 ± 1.87		
					1.18 ± 0 04	89 ± 16
44[a]	274.1	H	97.07			

[a] This sample of the protium compound was synthesized by the procedure used for the preparation of deuterium-labelled material. The extrapolated rate constant for the ordinary protium compound at 274.1°K is 96.1 × 10^{-5} sec^{-1}.

hydroxide in 95 % ethanol and the second-order asymmetric transformation of the racemic acid by brucine were carried out as described by Harris and Mitchell.[9]

The kinetics of the racemization in ethanol solution at temperatures in the interval −20 to 0°C were determined by following the change in optical rotation on a Perkin-Elmer 141 automatic reading polarimeter, using the mercury lines at 436 and 546 mμ as well as the sodium D line (runs 4 and 7, Table 2). The concentration of the ethanol solutions of the biphenyls ranged from 19.2 to 21.9 mg/ml solvent, except for that in run 4 (see Table 2) which was 27.2 mg/ml. There is no indication that the observed first-order rate constant is concentration-dependent in this range. A sample of the protium compound that had been prepared by the method used for the synthesis of the labelled substance had the same rate constant (within experimental error) as the protium compound prepared by the method of Harris and Mitchell.[9] (See run 44 in Table 2). A preliminary rate constant for each run was evaluated graphically from a semi-logarithmic plot. The first few points in some of the plots did not lie on the line, which indicated that thermal equilibrium had not been reached when these points were taken. Such points were discarded, and definitive values for all runs were then obtained by a least-squares treatment of the data on the Besk computer at the National Swedish Office for Administrative Rationalization and Economy. The kinetic data obtained in ethanol solution are presented in Table 2, the last column of which shows the isotopic difference in free energy of activation calculated according to eqn. (6).

$$\Delta\Delta F^{\ddagger} = \Delta F^{\ddagger}_{H} - \Delta F^{\ddagger}_{D} = RT \ln(k_D/k_H) \qquad (6)$$

The indicated errors are all maximum deviations.

The isotope effect on the rate of racemization was also determined in acetone, 0.5 N aqueous sodium hydroxide and dimethylformamide solutions. The results, which are presented in Table 3, show that the isotope effect ratio in these solvents is the same as that observed in ethanol. The rate constants in Table 3 were calculated by the least-squares method. Although it was desirable to determine the isotope effect over a greater range of solvent polarity, this was not feasible because of solubility problems and/or unsuitable

Table 3. Rate constants for racemization of 2,2′-dibromo-4,4′-dicarboxybiphenyl and its 6,6′-dideuterio derivative in various solvents

Run	Temp., °K	Isotope	Solvent	Concn (mg/ml solvent)	$10^5\ k$, sec^{-1}	k_D/k_H
33	272.9	H	Acetone	22.0	48.77	1.18
37		D	Acetone	21.4	57.56	
38	274.1	H	0.5 N NaOH	20.1	109.8	1.17
39		D	0.5 N NaOH	20.1	128.1	
42	274.1	H	DMF[a]	16.4	60.26	1.17
43		D	DMF[a]	16.7	70.39	

[a] Dimethylformamide.

freezing points. On these grounds, the following solvents of low polarity were found to be unusable for kinetic runs: hexane, isooctane, cyclohexane, dioxane, carbon tetrachloride, chloroform, benzene and toluene.

The rate of racemization appears to be influenced by the dipole moment of the solvent. This is not surprising since the dipole moment of 2,2′-dibromo-4,4′-dicarboxybiphenyl probably changes appreciably on going from the initial state "*cis*"-bromine configuration to the planar "*trans*" transition state. A solvent of high dipole moment increases the activation energy for racemization by stabilizing the initial state relative to the transition state.

DISCUSSION

A complete analysis of the significance of the observed effect requires its separation into $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ components, as indicated in eqn. (7).

$$RT \ln(k_D/k_H) = \Delta\Delta H^{\ddagger} - T\Delta\Delta S^{\ddagger} \quad (7)$$

In Table 4 the activation parameters calculated by a least-squares treatment of the rate data in Table 2 together with graphically estimated experimental errors are presented. It is obvious that a determination of $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$

Table 4. Activation parameters for racemization of 2,2′-dibromo-4,4′-dicarboxybiphenyl and its 6,6′-dideuterio derivative in ethanol solution.

Compound	E_a kcal/mole[a]	$\Delta H^{\ddagger}$ kcal/mole	$\Delta S^{\ddagger}$ *e.u.*
2,2′-Dibromo-4,4′-dicarboxybiphenyl	17.91 ± 0.13	17.38 ± 0.13	−8.8 ± 0.5
2,2′-Dibromo-4,4′-dicarboxybiphenyl-6,6′-d_2	17.87 ± 0.11	17.34 ± 0.11	−8.6 ± 0.4

[a] The Arrhenius activation energy calculated by a least-squares treatment of the rates in Table 2. The error limits were graphically estimated.

demands a higher reproduceability ($< \pm 0.5$ %) of the rate measurements than we have been able to achieve with the experimental difficulties involved in making polarimetric measurements below 0°C on optically labile compounds with low rotations. The maximum limits for $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ indicated by the data in Table 3 are of the order of ± 0.3 kcal/mole and ± 1 e.u., respectively. It is of course also possible to estimate maximum limits for $\Delta\Delta S^{\ddagger}$ by using the data in the last column of Table 2 and the thermodynamic relation between the entropy difference and the temperature variation of the free-energy difference,

$$\Delta\Delta S^{\ddagger} = -\delta\Delta\Delta F^{\ddagger}/\delta T \quad (8)$$

This indicates that the maximum limits of $\Delta\Delta S^{\ddagger}$ consistent with the experimental data are of the order of ± 1 e.u., in agreement with the value estimated above.

According to the theory of steric isotope effects as developed by Bartell,[3] the entire effect is assumed to be due to a difference in energy of activation (eqn. 4), and the isotopic activation entropy difference should consequently be zero. If this assumption is actually valid in the present case, *i.e.* if $\Delta\Delta E^{\ddagger} = \Delta\Delta H^{\ddagger} = \Delta\Delta F^{\ddagger}$, the agreement between theory and experiment is quite good when Howlett's potential [8] is used in the computation, but the possibility that this agreement may arise from a fortuitous combination of entropy and enthalpy effects cannot be disregarded.

An alternative interpretation of the observed isotope effect in terms of inductive differences between protium and deuterium is unsatisfactory. In the first place, it is unlikely that the inductive effect of hydrogen will change the energies of the initial and transition states appreciably differently in a biphenyl racemization, and thus the maximum isotopic inductive effect in this case is probably even less than the 1—3 % per deuterium reported for several reactions of aromatic molecules in which delocalization of charge into the aromatic system (ionization) takes place between the initial state and the transition state.[13–15] Secondly, the observed isotope effect is not sensitive to the properties of the solvent (see Table 3). A difference in inductive effect, *i.e.*, essentially a difference in the ability of protium and deuterium to support a movement of charge, might be expected to be influenced by solvent properties.

Hyperconjugative effects are certainly not likely to be of any importance in this case since the carbon-hydrogen bond is situated in the plane of the ring and the pertinent orbitals are thus mutually orthogonal.

In a theoretical calculation of the isotope effect which neglects steric and inductive effects, most of the vibrational frequencies would be assumed to cancel one another between the initial state and the transition state. The only difference which would be considered important involves the internal torsional oscillation of the two phenyl groups relative to one another. This mode is converted into the movement along the reaction coordinate when the transition state is reached. The moment of inertia for this movement depends on the angle between the planes of the two benzene rings. An exact treatment will not be attempted and it is probably sufficient to use the simple formula of Eyring and Cagle [16]

$$k_D/k_H = \sinh(hc\bar{\nu}_D/2kT)/\sinh(hc\bar{\nu}_H/2kT) \quad (9)$$

where h is Planck's constant, c the velocity of light, $\bar{\nu}$ the wave number, and k Boltzmann's constant. If it is assumed that the pertinent wave numbers are of the order of 200 cm^{-1} or less, $hc\bar{\nu}/2kT$ will be of the order of 0.5 or less. It is then a good approximation to write

$$k_D/k_H \approx \bar{\nu}_D/\bar{\nu}_H \quad (10)$$

The isotopic influence on the moment of inertia for the mode concerned will hardly exceed 2 %, which means that the frequencies will not differ by more than 1 %, and k_D/k_H will thus be between 0.99 and 1. "Non-steric" isotope effects are consequently not likely to affect the observed rate difference to any appreciable extent.

The present investigation may be considered an experimental approach to the little-known hydrogen-bromine non-bonded potential function, or rather

an approach to the second derivative thereof. The potential used in the above theoretical calculations is assumed to have a simple, purely repulsive form, which is certainly an oversimplification. One obvious extension of this investigation is an examination of the buttressing effect due to groups in the 3 and 3′ positions of the biphenyls studied in this work. The determination of the isotope effect in the racemization of such a buttressed system would be essentially a measurement of the second derivative of the same potential at closer approach of the non-bonded atoms. There is some risk, however, that increased crowding might eventually lead to deviations from planarity in the separate phenyl residues as well as deviations from the planarity of the transition state.[17]

EXPERIMENTAL PROCEDURES*

Melting points were determined on a Kofler Heizbank. Microanalyses were performed by A. Bernhardt, Mühlheim (Ruhr), West Germany.

2,2′-Dibromo-4,4′-dicarbomethoxybiphenyl was prepared and converted to the corresponding optically active acid as described by Harris and Mitchell.[9]

Trideuteriohypophosphorous acid was prepared[18] by exchange between commercial 50 % hypophosphorous acid (Merck, reagent grade) and 99.8 % deuterium oxide (Norsk Hydro), as follows: 50 % hypophosphorous acid (55 ml) was concentrated as far as possible at 5—10 mm below 50°C in a stream of nitrogen at the mechanical pump. Deuterium oxide (25 g) was added directly to the acid in the distilling flask, which was then stoppered and placed in a desiccator over silica gel for 48—72 h. To ensure a high degree of deuteriation, this procedure was repeated ten times, after which about 99 % of the protons in the hypophosphorous acid had been replaced by deuterium (according to NMR).

Methyl-3-nitro-4-iodobenzoate (II). Methyl-*p*-iodobenzoate (97.7 g, 0.37 mole), prepared by the reaction of potassium iodide with diazotized methyl-*p*-aminobenzoate,[19] was dissolved in concentrated sulphuric acid (135 ml) with stirring. Glacial acetic acid** (68 ml) was added to the stirred solution over a period of 15 min, during which time the temperature was maintained between 20—25° by means of a cold water bath. A mixture of concentrated sulphuric acid (51 ml) and 65 % nitric acid (51 ml, $d = 1.40$) was added fairly rapidly (*ca.* 15 min); the temperature was kept between 20—30° during this addition. The cooling bath was then removed and the temperature allowed to rise to 60° (*ca.* 10 min) from the heat of reaction. The mixture was vigorously stirred for another 50 min, and then poured into ice-water. The resulting yellow precipitate was filtered, washed thoroughly with water, and air-dried on the filter. Recrystallization from methanol afforded 82.2 g, m.p. 105—106° (lit.[19]: m.p. 104—106°). A second crop of 7.4 g, m.p. 103—105° was obtained from the mother liquor. From a total of 387.7 g of methyl-*p*-iodobenzoate, a total of 360.2 g (79.3 %) of methyl-3-nitro-4-iodobenzoate was prepared.

2,2′-Dinitro-4,4′-dicarbomethoxybiphenyl[19] *(III).* Methyl-3-nitro-4-iodobenzoate (II) (35 g) was melted in a 100 ml wide-mouthed Erlenmeyer flask heated in a Wood's metal bath. Copper bronze (21 g, Alfort and Cronholm No. 155) was added in small portions over a period of about 1 h. During this time, the temperature of the reaction mixture was maintained between 165—180° and that of the bath between 160—165°. When all of the copper bronze had been added, the bath was warmed to 175° over a period of 15 min, whereupon the flask was removed from the bath and allowed to cool to about 100°. The reaction mixture was treated with boiling chloroform several times, followed by filtration through a fine sintered glass filter. The chloroform was evaporated and the residue recrystallized from acetone-water. The yield was 17.5 g (85 %) of a pale yellow-green solid, m.p. 158—161° (lit.[20]: m.p. 159—160°).

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* We are grateful to Drs. M. M. Harris and Chua Cheung King Ling for sending us unpublished experimental procedures for some of the syntheses described here.

** The use of acetic acid in this nitration was suggested by Dr. K. D. Warren. By this means, the formation of a troublesome unidentified by-product mentioned by Chua and Harris[19] is prevented.

2,2'-Dibromo-4,4'-dicarbomethoxy-6,6'-dinitrobiphenyl (IV). 2,2'-Dinitro-4,4'-dicarbomethoxybiphenyl (III) (25 g, 0.069 mole) was dissolved in concentrated sulphuric acid (375 ml) in a three-necked flask equipped with a stirrer and a reflux condenser. Powdered silver sulphate (110 g, 0.35 mole) was added and the solution stirred until almost all of the silver sulphate had dissolved (*ca.* ½ h). Bromine (18 ml, 0.33 mole) was poured into the reaction mixture which was then stirred at room temperature for *ca.* 72 h, whereupon the reaction flask was placed in a water bath at 70° for ½ h during which time the bath was allowed to cool to 45°. The reaction mixture was poured with stirring into ice-water, treated with sodium pyrosulphite to destroy excess bromine, and then filtered with suction. The residue was washed thoroughly with water, air-dried on the filter, and then washed once with hot absolute ethanol (150 ml). The filter cake was transferred to a Soxhlet thimble, covered with glass wool to avoid spattering, and extracted overnight with absolute ethanol (*ca.* 1 liter). The extract was filtered through a fine sintered glass filter, and crystallization was then induced by scratching. The yield (first crop) was 23.9 g of light green crystals, m.p. 154—155°. Further crops were obtained by volume reduction of the mother liquor. From a total of 75 g of 2,2'-dinitro-4,4'-dicarbomethoxybiphenyl (III), a total of 83.7 g (77.6 %) of the dibromodinitro compound (IV) was prepared. (Found: C 37.17; H 1.93; N 4.93; Br 31.48. Calc. for $C_{16}H_{10}N_2O_8Br_2$: C 37.09; H 1.95; N 5.41; Br 30.85.)

2,2'-Dibromo-4,4'-dicarbomethoxy-6,6'-diaminobiphenyl (V). (General procedure).[19,21] 2,2'-Dibromo-4,4'-dicarbomethoxy-6,6'-dinitrobiphenyl (IV) (10—11 g) was dissolved in a hot mixture of 95 % ethanol (350 ml) and toluene (90 ml). W-2 Raney nickel* (1½ tsp.) was added with swirling, followed by hydrazine hydrate (99—100 %) dropwise at such a rate that a vigorous reaction was maintained without the application of heat. When the color of the reaction mixture had changed from its original red-brown to brown (after the addition of 15—20 ml of hydrazine hydrate), a second portion of Raney nickel was added (1 tsp.), the reaction flask was heated with a heating mantle to maintain boiling, and more hydrazine hydrate (5 ml) was added dropwise. The brown color slowly disappeared and the solution became apparently colorless. Filtration through a fine sintered glass filter revealed that the solution was actually light green. The volume was reduced by suction in a stream of nitrogen to *ca.* 100 ml (or until white crystals began to precipitate). The mixture was left in the refrigerator overnight, and a crude product (5—7 g) was deposited. Recrystallization from ethanol-water led to a nearly white solid, m.p. 166—168°. Second crops were usually rather brown and could not be satisfactorily recrystallized from ethanol-water. They were first purified by recrystallization from benzene, which produced beautiful plate-like crystals containing benzene of crystallization that was removed by precipitation of the amine from aqueous ethanol by the addition of water. A total of 65 g of the dibromodinitro compound (IV) was reduced in this way to 39.1 g (68 %) of 2,2'-dibromo-4,4'-dicarbomethoxy-6,6'-diaminobiphenyl (V). (Found: C 43.01; H 2.96; N 5.93; Br 33.93. Calc. for $C_{16}H_{14}N_2O_4Br_2$: C 41.95; H 3.08; N 6.12; Br 34.89.).

2,2'-Dibromo-4,4'-dicarbomethoxybiphenyl-6,6'-d_2 *(VI).* Deuterium chloride, prepared by the addition of deuterium oxide (3 ml) to an excess of hot benzoyl chloride[22] (80 ml), was led into cooled, stirred deuterium oxide (20 ml, 99.8 %) in a three-necked conical reaction flask with a medium sintered glass filter built into an angled sidearm. (All glassware used in this preparation had been previously dried in an oven at *ca.* 200° overnight). 2,2'-Dibromo-4,4'-dicarbomethoxy-6,6'-diaminobiphenyl (V) (4 g, 8.7 mmole) was dissolved in the deuterium chloride solution with stirring and slight warming (water-bath). This operation, as well as the remainder of the diazotization, was carried out in a nitrogen atmosphere. The solution of the dibromodiamine (V) was cooled to somewhat below 0°, and a solution of sodium nitrite (1.23 g, 17.8 mmole) in deuterium oxide (25 g, 22.7 ml) was added dropwise. The temperature was kept below 5° during the entire diazotization. When the addition of the sodium nitrite solution was complete, the addition funnel was rinsed with deuterium oxide (10 ml). The red-orange diazonium solution was rapidly filtered with suction through the sidearm filter into a one-liter flask containing a cold solution of trideuteriohypophosphorous acid (10 ml, *ca.*. 0.2 mole) in deuterium oxide

* Best results were obtained with rather freshly prepared Raney nickel (see *Org. Syn.* Coll. Vol. III, p. 181).

(50 g, 45.4 ml). The diazotization flask was rinsed with deuterium oxide (*ca.* 20 ml), and then the trideuteriohypophosphorous acid reaction mixture was diluted with deuterium oxide (130 ml). A soccer ball balloon was attached to the flask to allow for volume expansion due to the nitrogen evolved during the reaction, and it was placed in a cooled desiccator in the refrigerator. After 66 h, the flask was removed and left at room temperature overnight. The orange reaction mixture was filtered and the residue washed thoroughly with H_2O and air-dried on the filter. The orange filter cake was dissolved in chloroform (60 ml); petroleum ether (50 ml, b.p. range 60—71°) was added, which precipitated a fluffy, chartreuse-colored by-product that was not further investigated. The dark red solution was dried with calcium chloride and chromatographed on a column of alumina (25 × 4 cm). Elution with petroleum ether (b.p. range 60—71°)-chloroform mixtures (80—20 to 50—50 v/v) separated the desired product from several highly-colored impurities. The yield was 1.21 g (32 %) of white crystals after recrystallization from absolute ethanol. 2,2′-Dibromo-4,4′-dicarbomethoxybiphenyl-6,6′-d_2 (VI) has two melting points (113—114° and 124—126°) in agreement with those reported by Harris and Mitchell [9] for the non-deuterated compound (114° and 127—128°). An NMR spectrum showed that deuteration in the 6 and 6′ positions was satisfactorily complete (≥97 %); there were no detectable signals from protons in the 6 and 6′ positions.

2,2′-Dibromo-4,4′-dicarboxybiphenyl-6,6′-d_2 *and its resolution.* The hydrolysis of the deuterated ester (VI) with potassium hydroxide-95 % ethanol and the secondary asymmetric transformation of the racemic acid by brucine were carried out as described by Harris and Mitchell [9] for the non-deuterated compound.

Possible loss of deuterium from the heavy compound by hydrogen exchange was checked by means of NMR analysis. A sample of the deuterated acid recovered from several kinetic runs (in ethanol) was shown to have the same deuterium content in the 6 and 6′ positions as the original ester (VI).

NMR spectra. All NMR spectra were recorded by Dr. Sture Forsén on a Varian A60 instrument at the Royal Institute of Technology.

Kinetic experiments. All kinetic runs were done on a Perkin-Elmer 141 polarimeter. The error in each reading of the optical rotation is assumed to be about ± 0.002°. Obstruction of the light path due to the condensation of moisture from the the air was prevented by blowing streams of pre-cooled nitrogen onto the polarimeter cell windows through specially constructed brass mouthpieces. The pre-cooling was arranged by conducting the gas through a coil of thin polyethylene tubing in contact with the outer wall of the cell jacket and thermally insulated from the surrounding atmosphere.

The temperature was maintained within ± 0.1° at −20°C and within ± 0.2$_5$° at −10°C and above by a Lauda Tisch-Kryomate TK 30. Due to the construction of the polarimeter cell, it was not feasible to directly measure the inside temperature. Instead, the temperature of the circulating cooling liquid (ethanol) in the cell jacket was measured by two independent thermometers, the one as near the entrance of the cell jacket as possible, and the other as near the exit. The temperature inside the cell was taken to be the average of the readings of these two thermometers. The difference in these readings, which was never more than about 0.3°, was mainly due to the heat introduced by the nitrogen used to prevent condensation on the cell windows. This slight uncertainty in temperature does not influence the value of the isotope effect ratio since the rate constants for both labelled and unlabelled compounds were determined under the same conditions.

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