

Salt Effects on the Racemization of Biphenyls

II.* The Racemization of 6-Nitro-2,2'-dicarboxybiphenyl Dianion in Aqueous Salt Solutions

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Salt effects on the rate of racemization of 6-nitro-2,2'-dicarboxybiphenyl dianion in aqueous salt solutions at 50.7°C have been studied, and it has been found that in general added salts decrease the rate. The salt effects are treated as composite effects due to i) the indirect influence of the added salt on the activity of the biphenyl and ii) complex formation between the cation of the added salt and the carboxylate groups of the biphenyl. Independent evidence for complex formation has been obtained by titration in 1 M LiCl and 1 M KCl. Equilibrium constants for complex formation have been estimated from the kinetic data and found to be 0.45 for K⁺, 0.60 for Na⁺, and 1.31 for Li⁺, which is the order expected on the basis of the relative complexing abilities of these cations.

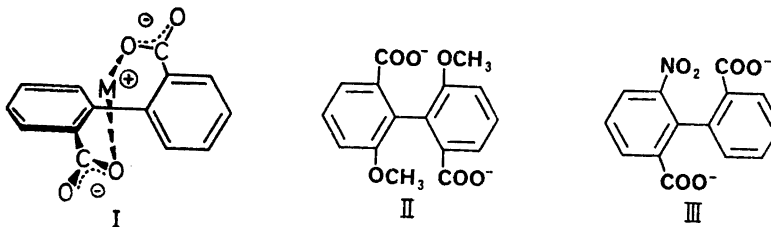
Salt effects on biphenyl racemization in aqueous solutions may be conveniently considered in terms of i) the indirect influence of the added salt on the activity of the biphenyl, and ii) the occurrence of specific, direct interaction(s) between the added salt and the center of reaction of the biphenyl, leading to the formation of new species. Effects of type i) may be separately studied by choice of a suitably substituted biphenyl with no charged groups in the 2 and 2' positions. In a recent investigation¹ of salt effects on the racemization of (+)-2,2'-diiodo-4,4'-dicarboxybiphenyl dianion, we obtained a linear correlation between the logarithm of the observed rate of racemization (k) and the ionic strength (J) up to about $J=1.0$. Such a correlation is expected for effects of type i) if the influence of the added salt is transmitted *via* an alteration in the ionic strength of the solution, and finds precedence in the work of Rieger and Westheimer² on the 2,2'-diiodo- and 2,2',3,3'-tetraiodo-5,5'-dicarboxybiphenyl dianions.

* For part I, see Ref. 1.

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Effects of type ii) are difficult, if not impossible, to study in the complete absence of indirect salt effects. If direct interactions between dissolved ions and the center of reaction in the configurational inversion of an appropriate biphenyl are likely to occur, any observed salt effect will most probably be due to the simultaneous operation of effects of both types.

The formation of a chelate complex (e.g. I) between the carboxylate groups and a metal cation was suggested by Leffler and Graybill³ to be part of the



explanation for their observed salt effects on the rate of racemization of 2,2'-dimethoxy-6,6'-dicarboxybiphenyl dianion (II). In the present work, we have investigated salt effects on the rate of racemization of another biphenyl with carboxylate groups at the center of reaction, 6-nitro-2,2'-dicarboxybiphenyl dianion (III), and have made an attempt to take both types of salt effects into account in our treatment of the kinetic data. Equilibrium constants for complex formation between III and several alkali metal cations (Li^+ , Na^+ , K^+) and tetramethylammonium cation (TMA^+) at 50.7°C have been estimated, and we have at the same time obtained indications that effects of type i) are of the same order of magnitude and in the same direction as those previously reported¹ for 2,2'-diiodo-4,4'-dicarboxybiphenyl dianion.

THEORETICAL CONSIDERATIONS

Salt effects that involve direct interaction between the dicarboxybiphenyl dianion (A^{2-}) and the cation (M^+) of the dissolved salt may be accounted for in terms of equilibria such as



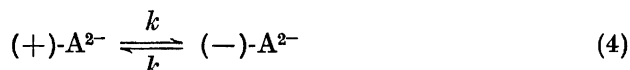
In this work, we have made the assumption that eqn. (2) and higher order complex equilibria may be neglected in view of the low concentration of A^{2-} in our solutions.* Complex formation with AH^- is considered negligible since in all cases the pH of the solutions for the kinetic runs was at least 9 (cf. Fig. 3). The equilibrium constant for complex formation according to eqn. (1) is defined by eqn. (3), where the concentrations are to be expressed in terms of molality (m).

* The total unweighed concentration of dicarboxybiphenyl was 0.006 M in all experiments involving added salts.

$$K = \frac{[\text{AM}^-]}{[\text{A}^{2-}][\text{M}^+]} \quad (3)$$

In the derivation that follows we assume that both A^{2-} and AM^- contribute to the observed optical rotation, but that only uncomplexed molecules undergo configurational inversion, *i.e.* that the rate of inversion of AM^- is negligibly small under our conditions.

Optically active A^{2-} inverts according to eqn. (4), and the rate



of racemization, k_{obs} , is obtained from eqn. (5)

$$-\frac{d\varphi}{dt} = k_{\text{obs}} \varphi \quad (5)$$

where φ is the measured optical rotation at time t . We have

$$\varphi = a[(+)\text{-A}^{2-}] - [(-)\text{-A}^{2-}] + b[(+)\text{-AM}^-] - [(-)\text{-AM}^-] \quad (6)$$

where a and b are the specific rotations of A^{2-} and AM^- , respectively. By eliminating $[(+)\text{-AM}^-]$ and $[(-)\text{-AM}^-]$ with eqn. (3) and differentiating eqn. (6) with respect to t we obtain (*cf.* eqn. (5)):

$$-\frac{d}{dt} ([(+)\text{-A}^{2-}] - [(-)\text{-A}^{2-}]) = k_{\text{obs}} ([(+)\text{-A}^{2-}] - [(-)\text{-A}^{2-}]) \quad (7)$$

Now $[(+)\text{-A}^{2-}]$ decreases according to eqn. (8)

$$-\frac{d[(+)\text{-A}^{2-}]}{dt} = k[(+)\text{-A}^{2-}] - k[(-)\text{-A}^{2-}] - \frac{d[(+)\text{-AM}^-]}{dt} \quad (8)$$

and $(-)\text{-A}^{2-}$ is formed according to a similar expression (eqn. 9)

$$\frac{d[(-)\text{-A}^{2-}]}{dt} = k[(+)\text{-A}^{2-}] - k[(-)\text{-A}^{2-}] + \frac{d[(-)\text{-AM}^-]}{dt} \quad (9)$$

Adding eqns. (8) and (9) and eliminating $[(+)\text{-AM}^-]$ and $[(-)\text{-AM}^-]$ with eqn. (3) gives

$$-\frac{d}{dt} ([(+)\text{-A}^{2-}] - [(-)\text{-A}^{2-}]) = \frac{2k}{1 + K[\text{M}^+]} ([(+)\text{-A}^{2-}] - [(-)\text{-A}^{2-}]) \quad (10)$$

An expression relating k_{obs} , k , and K may be obtained in a straightforward manner by combining eqns. (7) and (10):

$$\frac{1}{2} k_{\text{obs}} = k \frac{1}{1 + K[\text{M}^+]} \quad (11)$$

If the previously demonstrated dependence of k on the ionic strength $J^{1,2}$ (eqn. 12) is included, we obtain eqn. (13), where k_0 is the rate constant for inversion

$$k = k_0 \exp(B - B^\ddagger)J = k_0 \exp(B^\ddagger - B)a[\text{M}^+] \quad (12)$$

$$\frac{1}{2} k_{\text{obs}} = k_0 \frac{\exp(B - B^\ddagger)a[M^+]}{1 + K[M^+]} \quad (13)$$

of A^{2-} in the absence of salt effects (*i.e.* in an infinitely dilute solution), a is a constant for each type of added salt,* and the exponential factor represents the effect of the dissolved ions on the dielectric constant of the medium.^{1,4}

RESULTS

The rate of racemization of 6-nitro-2,2'-dicarboxybiphenyl dianion (III) in aqueous salt solutions was determined at $50.70 \pm 0.05^\circ\text{C}$. The salt concentration was varied from 0.012 m to 1.04 m, while the biphenyl dianion concentration was maintained at 0.006 M. The lowest uncomplexed metal ion concentration at which k_{obs} has been measured is thus *ca.* 0.01 m due to the cations accompanying III in aqueous solutions. In Fig. 1, k_{obs} is plotted *vs.* $[M^+]$, the concentration of the cation of the added salt. The plot indicates that k_{obs} is essentially independent of the *anion* of the added salt, since the points for both hydroxide and chloride solutions (for a given metal ion) fall roughly on the same line. This also shows that the salt effect is independent of the pH of the solution provided it is high enough to ensure that no appreciable amount of the half-neutralized acid (AH^-) is present.

A more convincing demonstration that k_{obs} is independent of the anion of the added salt is provided by the data in Table 1, where values for k_{obs}

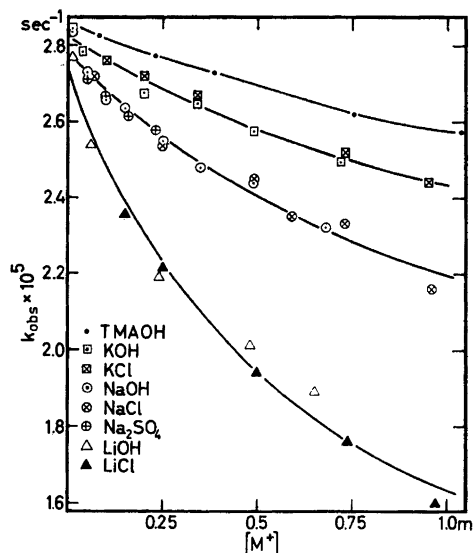


Fig. 1. Plot of $k_{\text{obs}} \times 10^5 \text{ sec}^{-1}$ *vs.* $[M^+]$ at 50.7°C for the racemization of III in aqueous solutions containing inorganic salts.

* $a=1$ for all of the salts used in this work with the exception of Na_2SO_4 for which $a=1.5$. The factor $a[M^+]$ represents J , neglecting the contribution of A^{2-} .

Table 1. Rate of racemization, k_{obs} , of the disodium salt of 6-nitro-2,2'-dicarboxybiphenyl at 50.7°C in various sodium salt solutions, all 0.25 m in Na^+ .

Salt	$k_{\text{obs}} \times 10^5 \text{ sec}^{-1}$	Standard error $\times 10^5$
NaCl	2.534	0.005
NaBr	2.533	0.006
NaI	2.576	0.003
NaOH	2.545	0.004
NaOAc	2.526	0.004
NaClO_3	2.559	0.004
NaNO_3	2.576	0.004
Na_2SO_4	2.611	0.005
Na_2CO_3	2.563	0.006

obtained in solutions of various sodium salts ($[\text{Na}^+] = 0.25 \text{ m}$) are listed. The total variation in k_{obs} is only about $\pm 2\%$ of the average value ($2.56 \times 10^{-5} \text{ sec}^{-1}$).

The experimental values of k_{obs} and $[\text{M}^+]$ were treated according to eqn. (13) by means of an iterative computer program which varied the parameters k_0 , $(B-B^\ddagger)$, and K to minimize * the quantity

$$\sum_i [(k_{\text{obs}})_i - (k_{\text{calc}})_i]^2$$

where $(k_{\text{calc}})_i$ is the calculated rate constant at $[\text{M}^+]_i$ for a given trial set of parameters.

The limits of variation of $(B-B^\ddagger)$ and K were chosen as $-1 < (B-B^\ddagger) < 1$ and $0 < K < 10$. The limits for $(B-B^\ddagger)$ are considered reasonable in view of our previous results¹ on indirect salt effects ($B-B^\ddagger = 0.44$ for 2,2'-diiodo-4,4'-dicarboxybiphenyl dianion).

The parameters obtained from the computer calculation are presented in Table 2. The upper half was obtained with constant k_0 and the lower half was obtained when k_0 was treated as a third parameter. It was found that $(B-B^\ddagger)$ and K are extremely covariant, and thus it is not possible to draw any significant conclusions about the "true" values of these parameters. However, the quantitative order of the equilibrium constants ($K_{\text{TMA}^+} < K_{\text{K}^+} < K_{\text{Na}^+} < K_{\text{Li}^+}$) is that expected on the basis of our knowledge of the relative complexing abilities of these cations.

The input value of $2k_0$ for the computer calculations was $2.865 \times 10^{-5} \text{ sec}^{-1}$, which had been estimated from the data plotted in Fig. 1. When only $(B-B^\ddagger)$ and K were varied, and k_0 was maintained constant, it was found that the average and maximum deviation of the $(B-B^\ddagger)$ values was 0.38 ± 0.21 (see the upper half of Table 2). Since an overall variation in k_0 of only ca. 5% gave a much lower maximum deviation for the $(B-B^\ddagger)$ values, the use of

* The minimization procedure in the program was written by Dr. J. P. Chandler, Physics Department, Indiana University. The program was modified for our use through the kindness of Mr. K.-I. Dahlqvist at the Royal Institute of Technology in Stockholm.

Table 2. Parameters in eqn. (13) obtained by computer treatment of the kinetic data. The upper half was obtained with constant k_0 and the lower half was obtained when k_0 was treated as a third parameter.

M ⁺	<i>K</i>	(<i>B</i> − <i>B</i> [‡])	2 <i>k</i> ₀ × 10 ⁵	$\sum_i [(k_{\text{obs}})_i - (k_{\text{calc}})_i]^2 \times 10^{10}$
TMA ⁺	0.3207	0.1721	2.865	9.1 × 10 ^{−5}
K ⁺	0.6635	0.3526	2.865	6.6 × 10 ^{−3}
Na ⁺	1.0586	0.4778	2.865	3.9 × 10 ^{−2}
Li ⁺	1.8785	0.5199	2.865	4.2 × 10 ^{−2}
TMA ⁺	0.2983	0.1563	2.861	8.2 × 10 ^{−5}
K ⁺	0.4512	0.2241	2.823	3.2 × 10 ^{−3}
Na ⁺	0.6049	0.2389	2.776	1.6 × 10 ^{−2}
Li ⁺	1.3091	0.3248	2.731	1.9 × 10 ^{−2}

k_0 as a third parameter in our treatment of the experimental data was considered acceptable.

According to the theory, the four curves in Fig. 1 should all give the same values for k_0 and ($B-B^\ddagger$). The discrepancy between the observed results and those predicted by eqn. (13) may be rationalised on the basis that K is not independent of the ionic strength, although we have assumed this to be the case for the sake of simplifying the theoretical treatment. The variation in K with ionic strength is the result of the influence of changes in ionic strength on activity coefficients. This is not expected to be significant enough to affect our conclusions regarding the relative values of the various K 's, and we thus consider this approximation justifiable. The value of ($B-B^\ddagger$) is taken to be 0.24 ± 0.09 , which is the average and maximum deviation of the values in the lower half of Table 2.

The data in Table 2 provide values for k_0 which are in rough agreement with that directly obtained by extrapolation on a plot of k_{obs} vs. the concentration of the dipotassium salt of III (see Fig. 2). It should be noted that Fig. 2 is a plot to zero concentration for all solutes while Fig. 1 is a plot which may only be extrapolated to zero cation concentration. A least-squares treatment of the data in Fig. 2 gives a value of $(1.44 \pm 0.02) \times 10^{-5} \text{ sec}^{-1}$ for k_0 .

The curves drawn through the experimental points in Fig. 1 were plotted using eqn. (13) with the computer-calculated parameters K , ($B-B^\ddagger$), and k_0 for each cation. Within the limits set by our experimental conditions (dilute solutions) and the theoretical considerations that led to eqn. (13), and bearing in mind the strong covariance of ($B-B^\ddagger$) and K , our interpretation of the observed salt effects on the rate of racemization of III in terms of indirect activity effects and complex formation is supported by the results presented here.

We have obtained independent evidence for complex formation from titrations⁵ on aqueous solutions of 6-nitro-2,2'-dicarboxybiphenyl (AH₂) in 1 M LiCl and 1 M KCl with LiOH and KOH, respectively. For these solutions, the following equilibria may be written:

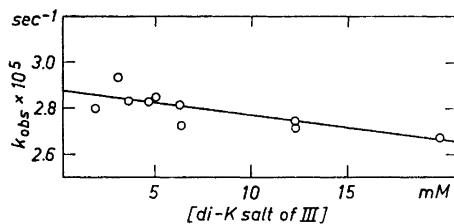


Fig. 2. Plot of $k_{\text{obs}} \times 10^5 \text{ sec}^{-1}$ vs. the concentration of the dipotassium salt of III at 50.7°C .

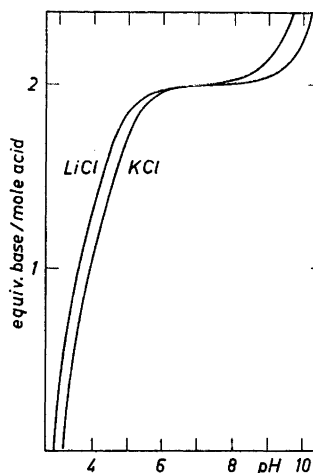
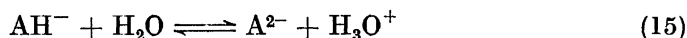
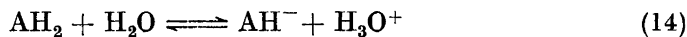


Fig. 3. Titration curves for 6-nitro-2,2'-dicarboxybiphenyl in 1 M LiCl and 1 M KCl.



A^{2-} is hereby released and may take part in complex formation as described by eqns. (1) and (2). The titration curves are presented in Fig. 3, from which it is apparent that a solution of the substrate AH_2 in 1 M LiCl is more acidic than a solution in 1 M KCl. This is attributed to the better complexing ability of Li^+ .⁵

DISCUSSION

As mentioned above, direct salt effects need not be considered in systems such as 2,2'-diiodo-4,4'-dicarboxybiphenyl dianion in dilute aqueous salt solutions,¹ and the observed increase of the racemization rate constant (k_{obs}) with increasing concentration may be satisfactorily accounted for by the simple expression (cf. eqn. 12)

$$\ln k_{\text{obs}} = \ln k_0 + (B - B^\ddagger)J \quad (16)$$

By definition^{1,4} $(B - B^\ddagger)$ is related to $\ln(f/f^\ddagger)$, and if $(B - B^\ddagger) > 0$ then $\ln(f/f^\ddagger) > 0$. Glasstone, Laidler and Eyring⁶ have pointed out that $\ln(f/f^\ddagger)$ may be equated with $-\Delta F_{\text{ext}}^\ddagger/RT$, where $\Delta F_{\text{ext}}^\ddagger$ is the free energy of activation "due to external factors, e.g., the medium in which the reaction occurs". Since we only change the salt concentration of the medium, we have used¹ the symbol $\Delta F_{\text{salt}}^\ddagger$ for $\Delta F_{\text{ext}}^\ddagger$ to emphasize the source of the "external factors" that influence the free energy of activation. Thus we may write

$$\ln(f/f^\ddagger) = -\Delta F_{\text{salt}}^\ddagger/RT = (\delta F_{\text{salt}} - \delta F_{\text{salt}}^\ddagger)/RT \quad (17)$$

where δF_{salt} is the difference in free energy of solvation for the initial state ion (or ion pair) in an ideal aqueous solution and in an aqueous solution of ionic strength J , and $\delta F_{\text{salt}}^\ddagger$ is the corresponding difference for the transition state ion. If $\ln(f/f^\ddagger) > 0$, this implies that $-\Delta F_{\text{salt}}^\ddagger > 0$, which in the case of 2,2'-diiodo-4,4'-dicarboxybiphenyl dianion was interpreted¹ in terms of a change in dipole moment on going from the initial state to the transition state. A similar straightforward interpretation is not possible in the present case.

In the system under study here, *direct* salt effects completely dominate those described by eqn. (16). We observe that the racemization rate *decreases* with increasing salt concentration in a manner satisfactorily explained by assuming the operation of indirect effects accompanied and overshadowed by complex formation³ (e.g. I), which i) effectively decreases the concentration of molecules undergoing configurational inversion and/or ii) stabilizes the initial state relative to the transition state. Similar conclusions were previously reached by Leffler and Graybill³ in their study of II, and we have found that their data for sodium, lithium and barium salts may also be accommodated by plots according to eqn. (13).

EXPERIMENTAL

Melting points were determined on a Kofler Hot-Stage Microscope or a Kofler Heizbank.

4-Nitrophenanthrenequinone. The mononitration of phenanthrenequinone was carried out as described by Kato and co-workers.⁷ The separation of 2-nitro- and 4-nitrophenanthrenequinone was performed according to Schmidt.⁸ The 4-nitrophenanthrenequinone thus obtained had m.p. 178°C; lit.^{7,8} m.p. 178°C.

6-Nitro-2,2'-dicarboxybiphenyl and its resolution. 4-Nitrophenanthrenequinone was oxidized to 6-nitro-2,2'-dicarboxybiphenyl by the method of Schmidt⁸ and the product then recrystallized from water. M.p. 250–253°C (decomp); lit.⁸ m.p. 248–250°C (decomp). The acid was resolved with morphine in ethanol according to Bell and Robinson⁹ except that the hydrolysis of the morphine salt was performed in the following way. The salt was ground with 10 equivalents of 2 N K₂CO₃ at room temperature. After 5 min the morphine was filtered off and the optically active acid was precipitated by carefully acidifying the filtrate with dilute HCl. The mixture was allowed to stand in the refrigerator for a few hours before filtering off the acid. This procedure was repeated twice to ensure complete separation of morphine and (–)-6-nitro-2,2'-dicarboxybiphenyl. The specific rotation of the acid was $[\alpha]_{436}^{50} = -792^\circ$ ($c = 4.70$ in 2 N K₂CO₃).

The test solutions were prepared as previously described.¹ In the case of tetramethylammonium hydroxide (TMAOH), (–)-6-nitro-2,2'-dicarboxybiphenyl was dissolved in b ml of 1.04 M TMAOH and 5.0 – b ml of H₂O was added to give the desired concentration. All salts used in the test solutions were *pro analysi* grade and the water had been deionised by passage through a Zerolit deioniser.

The kinetics of the racemization were determined on a Perkin-Elmer 141 polarimeter (cf. Ref. 1); each reaction was followed for about one half-life and about 15 readings were made during each run. In control runs in which the reaction was followed for about 7 half-lives, no drift in the first-order rate constant was observed. The rate constant k_{obs} and the standard error were calculated by a least-squares treatment of the kinetic data on a Data-SAAB D21 computer at the Department of Medical Biochemistry of the University of Göteborg. The magnitude of the standard error in k_{obs} is always less than 0.3 % of k_{obs} . The reproducibility of a given k_{obs} value is of the order of ± 1 %.

The titration curves were obtained by titrating 20 ml of a 0.001 M solution of 6-nitro-2,2'-dicarboxybiphenyl, 1 M in KCl or LiCl, with the corresponding hydroxide in deionised water with a Radiometer Titrigraph.

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