In order to prepare the possible unsymmetrical adducts, XII, XIII and XIV, a stepwise addition of the dienes to benzoquinone was attempted. When equimolar quantities of 1,2-dimethylenecyclohexane (I) and benzoquinone were refluxed in dioxane or benzene, a mixture of products was obtained. It was found, however, that the monoadduct, $\Delta^{2,8a(10a)}$-decahydroanthracene-1,4-dione (IX), was almost insoluble in boiling ether. Thus, when the reaction was carried out in ether, the monoadduct IX precipitated out as it was formed. The concentration of IX in solution was therefore very low, minimizing the formation of the diadduct II and producing a 94% yield of IX. In a similar manner, equimolar quantities of 4-methyl-1,2-dimethylenecyclohexane (V) and benzoquinone in ether produced a 96% yield of 6-methyl-$\Delta^{2,8a(10a)}$-decahydroanthracene-1,4-dione (X), and equimolar quantities of 4,5-dimethyl-1,2-dimethylenecyclohexane (VI) and benzoquinone in ether produced a 98% yield of 6,7-dimethyl-$\Delta^{2,8a(10a)}$-decahydroanthracene (XI).

If these monoadducts were treated with the appropriate diene, using dioxane as the solvent, a second molecule of diene added to the remaining activated double bond to produce the corresponding unsymmetrical diadducts. Thus, the monoadduct IX plus 4-methyl-1,2-dimethylenecyclohexane (V) produced an 84% yield of 2-methyl-$\Delta^{4a(14a),7a(11a)}$-octadecahydropentacene-6,13-dione (XII), and IX plus 4,5-dimethyl-1,2-dimethylenecyclohexane (VI) produced a 93% yield of 2,3-dimethyl-$\Delta^{4a(14a),7a(11a)}$-octadecahydropentacene-6,13-dione (XIII). In a similar reaction, the monoadduct XI plus the diene V produced an 83% yield of 2,3,9-trimethyl-$\Delta^{4a(14a),7a(11a)}$-octadecahydropentacene-6,13-dione (XIV). Thus, a very general method has been developed for the synthesis of both symmetrical and unsymmetrical pentacyclic quinone adducts that can be used as starting materials for the synthesis of substituted pentacenes.

Just as the octadecahydropentacenedione (II) was converted to pentacene (III), it was reasoned that tetracyclic derivatives, such as XV and XVI, could be converted to substituted napthacenes. These tetracyclic derivatives were available through a Diels–Alder reaction of a cyclic diene and 1,4-naphthoquinone. Thus, a solution of 1,4-naphthoquinone plus 4-methyl-1,2-dimethylenecyclohexane (V) in ether produced an 88% yield of 2-methyl-1,2,3,4,5,5a,6,11,11a,12-decahydronaphthacene-6,11-dione (XV). Similarly, 1,4-naphthoquinone plus 4,5-dimethyl-1,2-dimethylenecyclohexane (VI) produced a 93% yield of 2,3-dimethyl-1,2,3,4,5,5a,6,11,11a,12-decahydronaphthacene-6,11-dione (XVI). A general method for the synthesis of unsymmetrical naphthacene derivatives is now possible.

Experimental[7]

In a typical Diels–Alder reaction, 0.10 mole of the diene and 0.10 mole of the quinone were dissolved in 100 ml. of ether. After the reaction mixture had been heated under reflux for several hours, it was cooled and the precipitate was filtered off. In several experiments the solvent was evaporated to yield an additional quantity of adduct. In all runs except one, the crude adduct was recrystallized from ethanol to produce a white crystalline solid. Only 2,3,9-trimethyl-$\Delta^{4a(14a),7a(11a)}$-octahydropentacene-6,13-dione (XIV) was recrystallized from benzene.

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[7] All melting points are corrected. The authors are indebted to Vivian Kapacinski, Robert Keen and James French for the analyses.

COLLEGE PARK, MARYLAND

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NORTH CAROLINA]

Kinetics of Reactions of 2,4-Dinitrochlorobenzene with Some Familiar Nucleophilic Reagents[1]

BY J. F. BUNNETT AND GEORGE T. DAVIS

RECEIVED JANUARY 22, 1954

Rates of reactions of 2,4-dinitrochlorobenzene with five nucleophilic reagents in 60% dioxane have been measured or estimated. The following order of nucleophilic reactivity is established: thiophenoxide ion ≫ piperidine > methoxide ion > phenoxide ion ≫ hydroxide ion. Recognition of the low nucleophilic reactivity of the hydroxide ion allows rational explanation of several hitherto puzzling phenomena, including the Schotten–Baumann reaction.

In 1951, Bunnett and Zahler[2] commented on the paucity of information concerning the comparative activity of nucleophilic reagents in effecting aromatic substitution. The aim of the present research was to gather such information.

Our work was commenced with study of the reaction of hydroxide ion with 2,4-dinitrochlorobenzene. Except for some fragmentary reports,[3,4] no kinetic studies on the reactions of hydroxide ion with activated aryl halides have been published. The reason for this rather surprising gap in knowledge is evidently that alcohols have been the favorite solvents in which to measure the rates of aromatic nucleophilic substitution reactions, and solutions of hydroxide ion in alcohols act upon activated aryl halides to form principally ethers. To avoid this complication, we chose 60% dioxane:40% water (by volume) as the solvent for our studies; use of this solvent allows not only study of reactions with hydroxide ion, but also comparison of the reactivity of hydroxide ion with that of other nucleophilic reagents in the same solvent.

In Table I experiments are summarized which show the reaction of hydroxide ion with 2,4-dinitrochlorobenzene (equation 1) to be strictly second order, first order in hydroxide ion and first order in the aryl chloride. This result is of interest because

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[1] Presented to the Southern Regional Conclave, American Chemical Society, New Orleans, La., December, 1953.

[2] J. F. Bunnett and R. E. Zahler, *Chem. Revs.*, **49**, 340 (1951).

[3] J. Miller, *Chemistry and Industry*, 40 (1953).

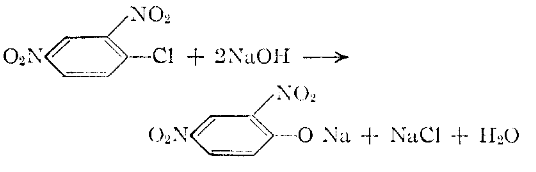
[4] (a) B. A. Bolto and J. Miller, *ibid.*, 640 (1953); (b) W. C. Spitzer and G. W. Wheland, THIS JOURNAL, **62**, 2995 (1940).

Table I

Kinetics of Reaction of 2,4-Dinitrochlorobenzene with Hydroxide Ion

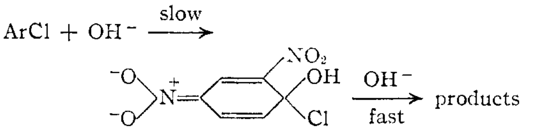
Run no.	$[ArCl]_0$, M	$[OH^-]_0$, M	Rate coefficient (l. mole^{-1} min.$^{-1}$) at 25.16°
1	0.0150	0.0300	0.0668
2	.0150	.0300	.0655
3	.0150	.0599	.0600
4	.0300	.0300	.0642

it throws light on the mechanism of the reaction.

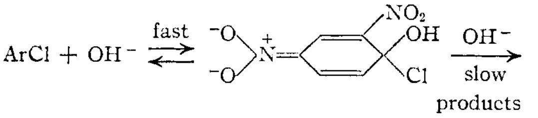


(1)

Two mechanisms, sketched in equations 2 and 3, require consideration. Both involve the formation



(2)



(3)

of a metastable intermediate, evidence for which view has been presented previously.[5] The kinetic evidence shows that the mechanism of equation 2, in which formation of the intermediate complex is the slow step, is correct, since the mechanism of equation 3 would require the reaction to be third order.[6,7] This result is in accord with the theoretical expectation[5] that formation of the intermediate complex should be rate-determining when the displaced group has greater potential anionic stability than the entering group.

Some attention was devoted to measuring the rate of reaction of hydroxide ion with 1-chloro-2-nitro-4-bromobenzene. This displacement is slow even at 99°, and it was found that the reaction of the base with the glass walls[8] of the reaction tubes was much faster. One trial run was made (at 99°) in polyethylene bottles, and this gave an approximate rate coefficient of 0.02 l. mole^{-1} min.$^{-1}$.

Our principal interest was in comparing the reactivity of nucleophilic reagents. Table II summarizes the results of our study of the rates of reaction of 2,4-dinitrochlorobenzene with hydroxide ion, phenoxide ion, piperidine, methoxide ion and thiophenoxide ion to form, respectively, sodium 2,4-dinitrophenoxide (equation 1), 2,4-dinitrodiphenyl ether, N-2,4-dinitrophenylpiperidine, 2,4-dinitroanisole and 2,4-dinitrodiphenyl sulfide.

Table II

Reactions of 1-Chloro-2,4-dinitrobenzene with Nucleophilic Reagents in 60% Dioxane

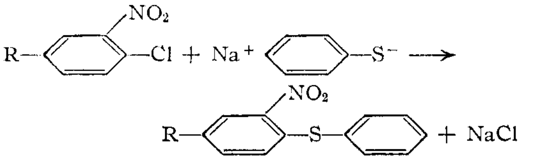
Reagent	Rate coefficient at 25.2° (l. mole^{-1} min.$^{-1}$)	ΔE (kcal./mole)	$\Delta S^{\ddagger}$ (cal./deg.)
OH^-	0.0662	17.5	−15.4
$C_6H_5O^-$	0.718[b]	14.7	−20.2
CH_3O^-	(2.2)[a,b]		
Piperidine	4.48	10.5	−30.5
$C_6H_5S^-$	(1300)[a]	(7.9)[a]	(−28)[a]

[a] Value estimated indirectly; see text. [b] See footnote 12.

Although the order of nucleophilic reactivity shown in Table II is essentially the same as that deduced by Bunnett and Zahler,[2] largely from qualitative considerations, we were nevertheless surprised to learn the very high reactivity of the thiophenoxide ion and the decidedly low reactivity of the hydroxide ion. We shall comment on the chemical significance of these discoveries presently.

It should be noted that there is, in Table II, a wide variation in the entropies of activation. The faster reactions have the lower entropies of activation, which means that if the entropy of activation had remained constant the spread of reactivity amongst the several reagents would have been much greater than it is.

In Table II, the rate coefficient for the reaction of thiophenoxide ion could not be measured directly because the reaction was, even at 0°, immeasurably fast. The coefficient was estimated indirectly (and approximately) by use of the Hammett relationship.[9] Bunnett, Moe and Knutson[10] have shown that the activating effects of the *p*-trifluoro-



(4)

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[5] Reference 2, pp. 297–302.

[6] A Referee has requested expansion of this conclusion. Three mechanisms for the passage of the complex and hydroxide ion into final products (dinitrophenoxide ion, chloride ion and water) are conceivable: (a) The E2 mechanism(Ingold's classification), involving concerted attack of hydroxide ion on the hydroxyl hydrogen and departure of the chloride ion; over-all third-order kinetics would be required. (b) A two-step bimolecular mechanism, involving first attack of hydroxide ion to form a di-negatively charged anion, and then departure of the chloride ion; this would also require over-all third-order kinetics. (c) The E1 mechanism, involving expulsion of chloride ion to form dinitrophenol which then reacts rapidly with hydroxide ion to form products: this would call for over-all second-order kinetics. Thus only if mechanism (3c) obtained would our conclusion be wrong.

Bearing in mind that the rate of (3c) could not be very large, otherwise one would have mechanism (2), we shall now estimate the rate of process (3b), and shall conclude that the rate of (3b) would not be small. The first step of (3b) is a proton exchange between oxygen atoms, an immeasurably fast type of process, and the second is the expulsion of chloride ion from the di-negatively charged anion. The second step is analogous to the expulsion of chloride ion from the complex it might form by becoming bonded to the carbonyl carbon of a ketone. Obviously, this second step would also be fast, and therefore we conclude that the rate of process (3b), a sequence of two fast steps, is great. Since the rate of (3c) cannot be large, mechanism (3) would require third order kinetics. Furthermore, it is clear that the second step of (b) must be faster than (c) because of the greater electron-furnishing mesomeric effect of the $-O^-$ group in the di-negatively charged anion than of the $-OH$ group in the mononegatively charged intermediate complex. Thus the (b) route is favored over the (c) route even as the final stage in mechanism (2).

[7] The kinetics are also compatible with the one-stage displacement mechanism favored by E. A. S. Cavell and N. B. Chapman, *J. Chem. Soc.*, 3392 (1953); our arguments against this mechanism have been presented elsewhere.[5]

[8] Pyrex glass reacted more rapidly with the base than did soft glass; this effect also has been observed by F. C. Foster and L. P. Hammett, This Journal, **68**, 1736 (1946).

[9] H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

[10] J. F. Bunnett, H. Moe and D. Knutson, This Journal, **76**, in press.

methyl and *p*-chlorine groups toward aromatic nucleophilic methoxydechlorination can be successfully correlated by the Hammett relationship, and so it is valid to use the relationship in the present very similar case. The necessary experimental data, pertaining to the reaction of sodium thiophenoxide with 4-substituted-2-nitrochlorobenzenes (equation 4), are displayed in Table III.

TABLE III

REACTIONS OF 4-SUBSTITUTED-2-NITROCHLOROBENZENES WITH SODIUM THIOPHENOXIDE

Group in 4-position	p-σ^*	Rate coefficient at 25.2° (l. mole^{-1} min.$^{-1}$)	ΔE (kcal./mole)	$\Delta S^{\ddagger}$ (cal./deg.)
CF_3	0.74[a]	13.6	10.6	−28
Cl	.23[b]	0.170	*c*	*c*

[a] Jaffe[9] did not give a σ^*-constant for CF_3; this value pertains to the ionization of anilinium ions (J. D. Roberts, R. L. Webb and E. A. McElhill, THIS JOURNAL, **72**, 408 (1950)). [b] A plain σ-value.[9] [c] For 1,4-dichloro-2-nitrobenzene, the rate coefficient was determined only at 25.2°.

From the data in Table III, ρ for the reaction is +3.7; this is about the magnitude that would be expected. From this ρ-value and the p-σ^* value for the nitro group (+1.27),[9] the rate coefficient for the reaction of 2,4-dinitrochlorobenzene with thiophenoxide ion is calculated to be 1300 l. mole^{-1} min.$^{-1}$. Since in reactions such as in equation 4 there is relatively little variation in entropy of activation as the group R is changed,[10] it is to be expected that the entropy of activation for the nitro-activated reaction will be about the same as that for the trifluoromethyl-activated reaction; thus the $\Delta S^{\ddagger}$ value in Table II. The energy of activation value for thiophenoxide in Table II was calculated from the estimated entropy of activation and rate coefficient.

In Table II, the rate coefficient for the reaction of methoxide ion could not be measured in 60% dioxane solvent because of uncertainty about the extent to which methoxide ion would interact with water in the solvent to form hydroxide ion. The rate coefficient for methoxide was estimated by comparing the reactivity of methoxide and phenoxide ions *vs.* 2,4-dinitrochlorobenzene *in methanol*, and assuming that the relative reactivity of these two reagents would be the same in 60% dioxane. This assumption is valid as an approximation because the two reagents are chemically similar and of the same charge type. At 25.2°, the rate coefficients in methanol were 1.49 l. mole^{-1} min.$^{-1}$ for methoxide,[10] and 0.479 l. mole^{-1} min.$^{-1}$ for phenoxide.[11] Methoxide reacted 3.11 times as fast as phenoxide, and so the rate coefficient 2.2 l. mole^{-1} min.$^{-1}$ has been assigned to methoxide ion in Table II.[12]

In connection with Table II, it is interesting to note that the strongest nucleophilic reagent (thiophenoxide ion) of the five we have considered is the weakest base, while the weakest nucleophilic reagent (hydroxide ion) is the strongest base.[13] This approximation to an inverse relationship between nucleophilic reactivity and basicity, within this limited set of reagents, shows that one must observe great caution in extending the usual parallelism between nucleophilic reactivity and basicity beyond comparison of reagents of very similar chemical type. Failure to observe such caution led Leahy and Miller[14] to conclude "that the difference in nucleophilic power of OH^- and OCH_3^- in methanol is very small and may be neglected."[15]

A further point of some interest is that the low nucleophilic reactivity of hydroxide ion as compared to methoxide ion finds a close parallel in the low nucleophilic reactivity of ammonia as compared to methylamine.[17] With 2,4-dinitrochlorobenzene in ethanol, methylamine reacts 800 times as fast as ammonia. While it is true that ammonia is a weaker base than methylamine, this vast difference in nucleophilic reactivity must relate to some special effect of replacing a hydrogen atom by an alkyl group. Whatever this effect is, it no doubt is also responsible for the high reactivity of methoxide as compared to hydroxide ion.

Our new knowledge of the low nucleophilic reactivity of the hydroxide ion makes intelligible several phenomena which hitherto have resisted satisfactory explanation. The first of these is the well-known fact that solutions of sodium or potassium hydroxide in methanol or ethanol act upon suitably activated aryl halides, nitro compounds, etc., to form mainly ethers, and not the phenols which would result from direct metathetical reaction of the aromatic compounds with hydroxide ion. Ethers are the predominant products even when the solvent contains a large percentage of water; for example, Richardson[18] found that *p*-chloronitrobenzene and potassium hydroxide in 60% ethanol: 40% water formed 71% of *p*-nitrophenetole and

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(11) T. J. F. Mattaar, *Rec. trav. chim.*, **41**, 103 (1922), reported 0.429 l. mole^{-1} min.$^{-1}$.

(12) In calculating the rate coefficients presented in Table II, interaction of the basic reagents with the solvent to form hydroxide ion has been assumed to be negligible. This assumption is not entirely valid, and therefore some of the values in Table II must be regarded as approximate. In estimating the extent of such interaction, we have noted that the dissociation constants of neutral acids decrease about 10^{-4}-fold as the solvent is changed from water to 60% dioxane (C. C. Lynch and V. K. La Mer, THIS JOURNAL, **60**, 1252 (1938)), while basic ionization constants of amines decrease about ten-fold for the same solvent change (J. C. James and J. G. Knox, *Trans. Faraday Soc.*, **46**, 254 (1950)). Accordingly, it is estimated that the interaction of thiophenoxide ion with the solvent to produce hydroxide ion would be negligible, interaction of piperidine would be negligible beyond about 25% reaction (*cf.* also Cavell and Chapman, ref. 7), while interaction of phenoxide ion with 60% dioxane would destroy about 10% of it with production of hydroxide ion. The rate coefficients in Table II for piperidine (based on approximately 25% to 80% reaction) and for thiophenoxide ion are therefore undisturbed by this effect. That for phenoxide ion is probably low by about 9%. Interaction of phenoxide ion with methanol (*cf.* J. W. Baker and A. J. Neale, *Nature*, **172**, 583 (1953)) would produce methoxide ion, a stronger nucleophilic reagent, and therefore the measured coefficient may be spuriously high. The over-all effect of these two corrections for reactions of phenoxide ion would be to *increase* the rate coefficient for methoxide in Table II.

(13) (a) J. Hine and M. Hine, THIS JOURNAL, **74**, 5266 (1952); (b) W. C. Woodland, R. B. Carlin and J. C. Warner, *ibid.*, **75**, 5835 (1953).

(14) G. D. Leahy and J. Miller, *Chemistry and Industry*, 40 (1953).

(15) Miller's[3] observation that 4-chloro-3,5-dinitrobenzoate ion reacts 7.6 times as fast with methoxide in methanol as with hydroxide in water has been interpreted to support the conclusion of Leahy and Miller. The interpretation disregards, however, the increase in the rate of a reaction between two anions which occurs with shift to a solvent of higher dielectric constant.[16]

(16) S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 431.

(17) Reference 2, p. 343.

(18) D. H. Richardson, *J. Chem. Soc.*, 522 (1926); other examples are cited in ref. 2, p. 348.

only 13% of *p*-nitrophenol. Clearly, the ethers result from reaction of the aromatic compounds with alkoxide ions generated by the equilibrium reaction shown in equation 5. The predominance of

$$\mathrm{OH^- + ROH \rightleftarrows RO^- + HOH} \qquad (5)$$

ether formation seemed especially perplexing when thought of in terms of the formerly prevalent belief that water was a stronger acid than methanol. Recent experiments[13] have shown, however, that methanol is a stronger acid than water, and that ethanol is nearly as acidic as water.[13a,19] It is now clear that in a solution prepared by adding potassium or sodium hydroxide to absolute methyl or ethyl alcohol, or even to one of these alcohols containing a few per cent. of water, the base is present almost entirely in the form of alkoxide ions. It is therefore reasonable that an ether should be formed by the action of this reagent on a suitable aromatic compound, and that the rate of substitution should be virtually the same as when a sodium or potassium alkoxide in an anhydrous alcohol is the reagent.[20] However, in a solution containing a large percentage of water, as in the example from Richardson's work cited above, an additional factor must be operating in favor of ether formation.

A rough calculation, using Caldin and Long's[19] equilibrium constant, shows that in Richardson's solution of potassium hydroxide in 60% ethanol, hydroxide ions outnumbered ethoxide ions about 3:1. Only the very low nucleophilic reactivity of hydroxide ions as compared to ethoxide ions kept phenol formation from being the preponderant reaction in this solution. Thus the phenomenon of predominant ether formation is explained by two effects, both working in the same direction: the recently recognized acidity of methyl and ethyl alcohols, and the low nucleophilic reactivity of hydroxide ion established by our experiments.

Beringer and his colleagues[21] have recently reported that the reaction of diphenyliodonium bromide with hydroxide ion produces mainly diphenyl ether and only a small amount of phenol, while 2- and 3-nitrodiphenyliodonium bromides and hydroxide ion gave the nitrophenols in good yields. The predominant formation of diphenyl ether is now easily understood because phenoxide ion, the product of substitution induced by hydroxide ion, is a much stronger nucleophilic reagent and therefore participates forthwith in a second stage of substitution to form diphenyl ether. On the other hand, the 2- and 3-nitrophenoxide ions are weakened as nucleophilic reagents by their nitro groups,[14,22] and therefore collect in the reaction mixture to be isolated as products.

Swain and Scott[23] have demonstrated that relative nucleophilic activity toward carbon remains essentially unchanged, amongst a group of reagents, as the substrate is changed, for example, from an alkyl halide to a carboxylic acid chloride or a sulfonic acid ester. Their study did not consider substitutions at aromatic carbon atoms, but there is reason to believe that their principle can be extended to this domain. For example the thiophenoxide ion, which we find to be some 580 times as reactive as methoxide toward 2,4-dinitrochlorobenzene, has been found[24] to react about 240 times faster than ethoxide ion with 3,3-dichloro-1-propene (both S_N2 and S_N2'), and it also has been reported[25] that thiophenoxide surpasses methoxide in effecting bimolecular substitution in ethylene dibromide. It follows, then, that the order of nucleophilic reactivity toward 2,4-dinitrochlorobenzene established by our experiments should also apply to aliphatic substitutions brought about by these same reagents.

This corollary leads to a rational explanation of the fact that, in the Schotten–Baumann reaction, the acid chloride reacts preferentially with the amine or alcohol being acylated and not with the aqueous alkali present in large excess. Hammett's suggestion[26] that the success of the procedure was due to low nucleophilic reactivity of the hydroxide ion has been rejected recently by Swain[23,27] who averred that the nucleophilic reactivity of hydroxide is not abnormally low and explained the Schotten–Baumann reaction on solubility grounds. He explained that the reaction is usually run in a non-homogeneous system, that acylation occurs in the non-aqueous phase, and that hydroxide ion is unable to enter this phase. Our results show, however, that the hydroxide ion is a weak nucleophilic reagent compared to the alkoxide ions or amines[28] which do in fact react with the acid chloride. Therefore, even in a homogeneous system one would expect the acid chloride to participate preferentially in ester or amide formation. Thus, a complete explanation of the Schotten–Baumann reaction involves consideration of both the solubility relationships advocated by Swain and the low nucleophilic reactivity of hydroxide ion established by our experiments.

The fact that dimethyl sulfate can be employed to methylate amines, phenoxide ions, carbohydrates, etc., in the presence of aqueous alkali is also to be explained on similar grounds.

Acknowledgments.—We thank the U. S. Army, Office of Ordnance Research, for financial support of this research. We are also grateful to Dr. Richard J. Morath who isolated and identified most of the reaction products.

Experimental

Materials.—2,4-Dinitrochlorobenzene, 1,4-dichloro-2-nitrobenzene, 4-chloro-3-nitrobenzotrifluoride,[29] thiophenol, phenol and piperidine were commercial products repurified. 1,4-Dioxane was purified by the method of Beste and Hammett.[30] The aqueous dioxane used for rate studies

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[19] E. F. Caldin and G. Long, *Nature*, **172**, 583 (1953), report the equilibrium constant of reaction 5 (R = C_2H_5) to be 0.7.

[20] Reference 2, pp. 347–349.

[21] F. M. Beringer, A. Brierley, M. Drexler, E. M. Gindler and C. C. Lumpkin, This Journal, **75**, 2708 (1953).

[22] L. C. Raiford and J. C. Colbert, *ibid.*, **48**, 2652 (1926).

[23] C. G. Swain and C. B. Scott, *ibid.*, **75**, 141 (1953).

[24] P. B. D. de la Mare and C. A. Vernon, *J. Chem. Soc.*, 3331 (1952).

[25] J. Hine and W. H. Brader, This Journal, **75**, 3964 (1953).

[26] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 303.

[27] C. G. Swain, speech to Organic Chemistry Symposium, American Chemical Society, Ann Arbor, Mich., June, 1953.

[28] It should be noted, however, that there are vast differences in nucleophilic activity amongst amines.[17]

[29] A gift from the Hooker Electrochemical Co., to whom we are thankful.

[30] G. W. Beste and L. P. Hammett, This Journal, **62**, 2481 (1940).

was prepared by mixing 8100 cc. of purified dioxane with 5400 cc. of carbon dioxide-free distilled water; both ingredients were at 23–24° and the mixing operation was performed at that temperature.

Rate Measurements.—For fast reactions (reactions of piperidine and sodium thiophenoxide with 2,4-dinitrochlorobenzene and 4-chloro-3-nitrobenzotrifluoride), the reacting solution was made up in a volumetric flask immersed in the thermostat using ingredients all at thermostat temperature. Zero time was not accurately recorded. The flask was briefly removed from the thermostat, quickly shaken and returned. Samples (8 or 9 per run) were withdrawn by a fast-delivery pipet and discharged into an excess of dilute sulfuric acid, the time of release from the pipet being recorded. In the case of runs at 0°, the pipet was chilled by ice before being used and between withdrawals of samples.

For the other reactions, the reacting solution was made up in a volumetric flask at 23° and then dispensed by means of a pipetting device into nitrogen-filled, rubber-stoppered test tubes (9 or 10 per run). All the tubes were placed in the thermostat at once. Reaction was stopped by addition of an excess of dilute sulfuric acid to the reacting solution in each tube, the time of addition being recorded. This technique required corrections to be made for thermal expansion or contraction of the solution.

Thermostats were constant to ±0.02°, and their temperatures were checked against thermometers certified by the Bureau of Standards.

The extent of reaction in all samples was estimated by potentiometric titration of the chloride ion liberated, using a silver electrode *vs.* glass electrode cell. Since thiophenol interfered with this cell, it was necessary to extract each sample from thiophenoxide runs with carbon tetrachloride and then ether before titration; the titrations were then fairly satisfactory, though the precision in these measurements was less than in the others.

In all runs the initial concentration of the aryl chloride was about 0.015 *M*. In runs with phenoxide or thiophenoxide, the initial concentration of the nucleophilic reagent equalled that of the aryl chloride; in runs with piperidine or hydroxide (except as noted in Table I), it was double. Rate coefficients were calculated from the slope of the plot of $1/(a - x)$ *vs.* time, the slope being, respectively, k and $2k$ for the two cases mentioned above. (Appropriate logarithmic expressions were used in calculation of runs 3 and 4 of Table I). The plots were linear without regular curvature or much scatter of points, and covered as little as 40% reaction to as much as 80% reaction. Slopes were determined by the method of least squares with each point weighted according to the fourth power of the per cent. of aryl chloride unreacted.

Duplicate runs were made for each reaction at each temperature (except for runs 3 and 4 in Table I) and the two determinations agreed within an average deviation of one per cent. except for the reaction with phenoxide ion in methanol (1.7%) and for runs with thiophenoxide ion (2.5% to 6%).

The following rate coefficients have not already been given in the tables or text (all in units of l. mole^{-1} min.$^{-1}$): 2,4-dinitrochlorobenzene with sodium hydroxide at 45.05°, 0.419 with sodium phenoxide at 0°, 0.0733; with piperidine at 0°, 0.874; 4-chloro-3-nitrobenzotrifluoride with sodium thiophenoxide at 0°, 2.62.

Product Identification.—The following expected products were isolated from samples of the reacting solutions which were allowed to stand a long time unquenched: 2,4-dinitrophenol, m.p. 113–114°; 2,4-dinitrodiphenyl ether, m.p. 69.5–70°; N-2,4-dinitrophenylpiperidine, m.p. 91–92.5°; 2,4-dinitrodiphenyl sulfide, m.p. 121°; 4-chloro-2-nitrodiphenyl sulfide, m.p. 83–84° (lit.[31] 86°); 2-nitro-4-trifluoromethyldiphenyl sulfide, m.p. 71–72°.[32]

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(31) J. D. Loudon and N. Shulman, *J. Chem. Soc.*, 1618 (1938).

(32) G. W. Stacy and C. R. Bresson have recently prepared and characterized 2-nitro-4-trifluoromethyldiphenyl sulfide; they found m.p. 72.5–73.5° (private communication).

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The Mechanism of Action of the Enzyme Hydrogenase[1]

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Both whole cells and cell-free extracts of *Proteus vulgaris* catalyze the exchange reaction between heavy water and hydrogen and the conversion of para to normal hydrogen. Both reactions follow first-order kinetics and are equally affected by the inhibitors, oxygen and cyanide. While cells, suspended in H_2O, catalyze the conversion of para- to orthohydrogen, no conversion occurs if D_2O is substituted for H_2O. These experiments are all in accord with the following mechanism for the mode of action of hydrogenase: $H_2 + E \rightleftarrows H{:}E^- + H^+$, where E represents the enzyme. We postulate that $H{:}E^-$ is the active reducing agent.

The enzyme hydrogenase has been found in several bacterial species and is presumably present whenever hydrogen gas is either utilized or produced by them. The similarity between the action of this enzyme and platinum hydrogenation catalysts was pointed out by Green and Stickland[4,5] who showed that the extent of reduction of N,N′-dimethyl, γ,γ′-dipyridyl ($E_0' = -0.446$) is the same with *B. coli* and colloidal platinum. It was suggested that the reaction was

$$H_2 \rightleftarrows 2H\cdot \qquad (1)$$

$$H\cdot \rightleftarrows H^+ + e \qquad (2)$$

In 1934, Farkas, Farkas and Yudkin[6] showed that the hydrogenase in *B. coli* is capable of catalyzing the exchange reaction between D_2O and molecular hydrogen. This exchange reaction has been studied in detail in *Proteus vulgaris* by Hoberman and Rittenberg[7] and Farkas and Fischer.[8]

When *B. coli* was suspended in H_2O in an atmosphere of ortho deuterium,[9] Farkas[10] observed that

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(2) National Science Foundation Predoctoral Fellow, 1953–1954. This report is from a dissertation to be submitted by Alvin I. Krasna in partial fulfillment of the requirement for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

(3) On leave, 1953–1954; The Institute for Advanced Study, Princeton, N. J.

(4) D. E. Green and L. H. Stickland, *Biochem. J.*, **28**, 898 (1934).

(5) L. H. Stickland, *Nature*, **133**, 573 (1934).

(6) A. Farkas, L. Farkas and J. Yudkin, *Proc. Roy. Soc.* (*London*), **B115**, 373 (1934).

(7) H. Hoberman and D. Rittenberg, *J. Biol. Chem.*, **147**, 211 (1943).

(8) L. Farkas and E. Fischer, *ibid.*, **167**, 787 (1947).

(9) A discussion of the various nuclear spin isomers of hydrogen and deuterium can be found in "Orthohydrogen, Parahydrogen and Heavy Hydrogen" by Farkas.[11] In this paper, the term normal hydrogen denotes the equilibrium mixture at room temperature of ortho- and parahydrogen (25% para, 75% ortho) and the term normal deuterium denotes the equilibrium mixture at room temperature of ortho and para deuterium (67% ortho, 33% para). The term parahydrogen is used for hydrogen containing more than 25% parahydrogen. H_2(o) represents orthohydrogen, H_2(p), parahydrogen and H_2(n), normal hydrogen. The reaction which converts H_2(p) to H_2(n) we shall call the conversion reaction; the reaction between hydrogen gas and deuterium oxide or between deuterium gas and normal water we shall call the exchange reaction.

(10) A. Farkas, *Trans. Faraday Soc.*, **32**, 922 (1936).