Phase-Transfer-Catalyzed Azo Coupling Reactions in Two-Phase Systems

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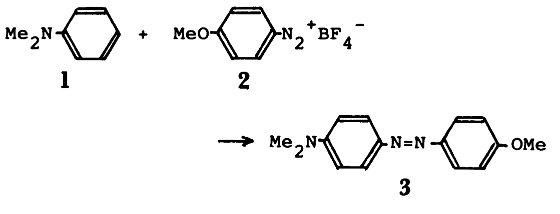
The azo coupling reaction of *p*-methoxybenzenediazonium tetrafluoroborate with *N,N*-dimethylaniline has been investigated in a water–1,2-dichloroethane system. It has been found that, among the several additives examined, the phenolate ion, generated from picric acid or 2,4-dinitro-1-naphthol, acted as an effective phase-transfer catalyst. Further, the reaction of *p*-diethylaminobenzenediazonium tetrafluoroborate with dimedone, an active methylene compound, has also been investigated in the same two-phase system; a remarkable acceleration in the rate was observed in the presence of tetraalkyl onium salts, and even in their absence.

Today, phase-transfer catalysis is a well-established technique in preparative chemistry.[1] However, it has been confined almost exclusively to nucleophilic or base-mediated reactions. On the other hand, azo coupling reactions under phase-transfer-catalyzed conditions have been intensively studied in recent years as a model for electrophilic substitution reactions. In such chlorinated hydrocarbons as chloroform and dichloromethane, pyrroles, arylamines, and phenol can easily react with diazonium salts in the presence of crown ether,[2] tetramethylammonium chloride,[3] tetraarylborate ion,[4] and/or silica gel,[5] showing their function as liquid-solid phase-transfer catalysts (PTC). It has also been claimed that tetraarylborate[4] and dodecylbenzenesulfonate[6] ions act as a PTC for the azo coupling reactions of arylamines in a water–dichloromethane two-phase system, although the effect of the latter might complicate the reaction by micelle formation.[7,8]

Here we wish to report that picrate and 2,4-dinitronaphtholate ions, as well as perchlorate and periodate ions, act as efficient anionic PTCs for an azo coupling reaction with an arylamine in a liquid-liquid two-phase system. Reactions with an active methylene compound in two-phase systems are also described in which a remarkable acceleration in the rate was observed in the presence of tetraalkyl onium salts, and even their absence.

Results and Discussion

Reaction with *N,N*-Dimethylaniline. The reaction of *N,N*-dimethylaniline (**1**), a neutral substrate, with *p*-methoxybenzenediazonium tetrafluoroborate (**2**) in the water–1,2-dichloroethane system was examined.



(1)

The rate measurements were performed by monitoring the absorbance at 410 nm due to **3**, in the presence of a 50-fold excess of **1** compared to **2**. Under these conditions, an excellent pseudo-first-order kinetic plot with respect to **2** was obtained with a correlation coefficient (r) greater than 0.99 in the range from 10 to 70% reaction in each run (Eq. 2):

$$\text{Rate} = k'[\text{Ar}-\text{N}_2^+]. \tag{2}$$

The influence of the stirring speed on the reaction rate was checked in the two-phase system (Fig. 1). Stirring at rates higher than about 600 rpm had essentially no effect on the reaction rate, suggesting that a transfer of the diazonium ion from the aqueous to the organic phase is fairly fast and that the rate is determined by the reaction in the organic phase.

The rates in the presence of several additives at 700 rpm are summarized in Table 1, including those in homogeneous solutions (Runs 1 and 2). The effects of arenesulfonate ions as PTCs were small (Runs 10 and 11). On the other hand, it is noteworthy that picric acid and 2,4-dinitro-1-naphthol exhibited considerable acceleration in the rate: the rate was proportional to the catalyst concentration, as has been observed in other phase-transfer-catalyzed azo coupling reactions.[4] In general, a phenol blocked by a substituent at the 2-, 4-, and 6-positions reacts with a diazonium ion to form covalently-bonded diazoether

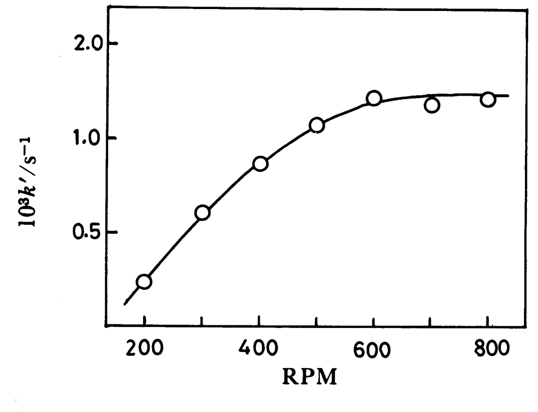


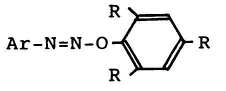
Fig. 1. Effect of stirring speed (RPM) on the reaction rate in the water/1,2-dichloroethane at 15 °C: $ArN_2^+NF_4^-$ 1.0×10^{-4} mol dm^{-3}; PhNMe$_2$ 5.0×10^{-3} mol dm^{-3}; picric acid 1.0×10^{-5} mol dm^{-3}.

Table 1. Pseudo-First-Order Rate Constants for the Reaction of *p*-Methoxybenzenediazonium Tetrafluoroborate with *N*,*N*-Dimethylaniline in Water–1,2-Dichloroethane System at 15 °C[a)]

Run	Additive/mol dm^{-3}	k'/s^{-1}
1[b)]	—	2.1×10^{-4}
2[c)]	—	3.3×10^{-3}
3	—	3.6×10^{-5}
4	Picric acid (3.6×10^{-5})	1.0×10^{-3}
5	Picric acid (6.0×10^{-5})	1.4×10^{-3}
6	Picric acid (3.0×10^{-4})	4.0×10^{-3}
7	Picric acid (6.0×10^{-4})	6.2×10^{-3}
8	Picric acid (3.0×10^{-3})	3.1×10^{-2}
9	2,4-Dinitro-1-naphthol (3.0×10^{-3})	1.2×10^{-2}
10	2,4,6-Trinitrobenzenesulfonic acid (3.0×10^{-3})	3.6×10^{-3}
11	Sodium 1-naphthalenesulfonate (3.0×10^{-2})	1.7×10^{-4}
12	Sodium perchlorate (6.0×10^{-5})	2.4×10^{-4}
13	Sodium perchlorate (1.2×10^{-3})	3.4×10^{-4}
14	Sodium perchlorate (1.2×10^{-2})	6.1×10^{-4}
15	Sodium perchlorate (6.0×10^{-2})	1.3×10^{-3}
16	Sodium periodate (3.0×10^{-2})	5.2×10^{-4}
17	Sodium chlorate (3.0×10^{-2})	7.6×10^{-5}

a) Reaction conditions: at 700 rpm; $ArN_2^+BF_4^-$ 1.0×10^{-4} mol dm^{-3}; $PhNMe_2$ 5.0×10^{-3} mol dm^{-3}. b) In aqueous methanol (1 : 1, v/v). c) In 1,2-dichloroethane.

(**4**).[9)] Indeed, no catalytic effect was observed for 2,4,6-



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trichlorophenol; however, it immediately gave a compound with an absorption maximum at 357 nm, presumably due to its diazoether. On the other hand, it seems likely that a diazonium ion forms an ion pair with a picrate or dinitronaphtholate ion of low nucleophilicity, which migrates into the organic phase. The reactivity of the diazonium ion is thereby increased by a minimization of solvent interactions. The phenolate ion liberated in the organic phase is used in the next PTC cycle, i.e., it forms an ion pair with a protonated arylamine formed by proton abstraction from a σ-complex. It then reverts to the aqueous phase. It is also noteworthy that the rates (Runs 6—8) in the presence of picrate ion in a two-phase system exceed that of the diazonium tetrafluoroborate in dichloroethane (Run 2), suggesting that the reactivity of the diazonium ion with the picrate ion as a counter ion is higher than that with the tetrafluoroborate ion. The higher reactivity of the diazonium ion with the picrate ion may be ascribed to its weak ion-pairing; this is because a strong ion-pairing would be expected to cause a decrease in the electrophilicity of the diazonium ion.[10,11)]

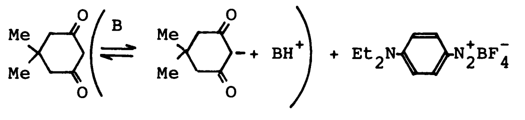
Table 2. Pseudo-First-Order Rate Constants for the Reaction of Potassium 5,5-Dimethyl-1,3-cyclohexanedionide with *p*-Diethylaminobenzenediazonium Tetrafluorobrate at 25 °C[a)]

Run	Solvent	18-Crown-6	k'
		mol dm^{-3}	s^{-1}
1	H_2O	None	3.7×10^{-6}
2	MeOH	None	2.5×10^{-6}
3	MeCN	None	9.3×10^{1}
4	MeCN	2.0×10^{-3}	2.3×10^{2}
5	CH_2Cl_2	3.0×10^{-3}	3.5×10^{2}
6	$CHCl_3$	2.8×10^{-3}	1.2×10^{2}
7	THF	3.3×10^{-3}	6.5×10^{1}
8	$ClCH_2CH_2Cl$	2.9×10^{-3}	1.4×10^{2}
9	$ClCH_2CH_2Cl$	7.9×10^{-3}	3.0×10^{2}
10	$ClCH_2CH_2Cl$	2.3×10^{-2}	2.9×10^{1}
11	$ClCH_2CH_2Cl$	5.8×10^{-2}	6.8

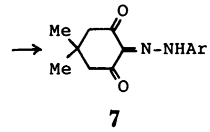
a) Reaction conditions: $ArN_2^+BF_4^-$ 5.0×10^{-5} mol dm^{-3}; Substrate 2.5×10^{-3} mol dm^{-3}.

The addition of such inorganic ions as perchlorate (Runs 12—15) and periodate (Run 16), which are of high extraction capability toward common onium cations into chlorinated hydrocarbon,[12)] also accelerated the two-phase reaction. A similar acceleration by iodide ion to that by the perchlorate ion was observed. However, the iodide ion seems to be of no practical significance, since it catalyzed the homolytic decomposition[13)] of the diazonium ion giving an impure azo compound.

Reaction with Dimedone. Secondary, the reaction of 5,5-dimethyl-1,3-cyclohexanedione (dimedone **5**, pK_a=5.2[14)]), an active methylene compound, with *p*-diethylaminobenzenediazonium tetrafluoroborate (**6**) was selected, since the rate could be measured directly in all the solvent systems investigated.



5 **5′** **6**



(3)

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Prior to the study in the two-phase system, the solvent effects on the reactivity of the carbanion (**5′**) were investigated in homogeneous solutions. The potassium salt of **5′** was completely solubilized into a solvent by adding 18-crown-6 (hereafter called crown), except for water and methanol. After a solution of **6** in the same organic solvent was added into this solution, the absorbance at 490 nm due to product **7** was followed under the pseudo-first-order kinetic conditions (Table 2). In contrast to the azo coupling reaction with *N*,*N*-dimethylaniline, in which no significant solvent effects have been observed,[15] it can be seen that there are large differences in the rates between water and organic solvents; e.g., reactions in chlorinated hydrocarbons proceed faster than in water by ca. an order of magnitude of 8. Under these conditions, in which nearly an equivalent of the crown to the substrate was present, the crown probably tended to complex with the potassium salt of **5′** rather than **6**, giving a "naked carbanion" of high reactivity. The addition of a large excess of the crown, however, retarded the reaction (Runs 10 and 11), due to a partial conversion of the diazonium ion into its unreactive complex with the crown.[16]

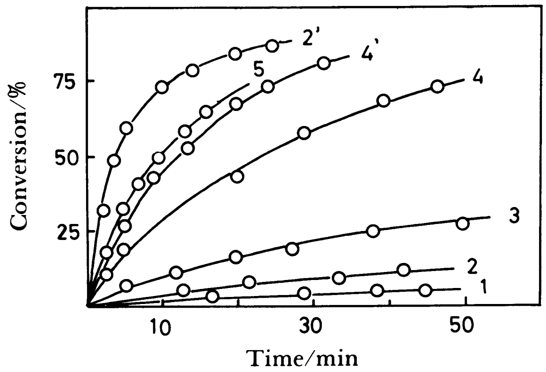
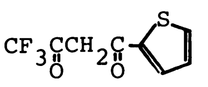
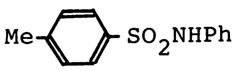
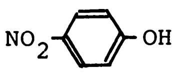
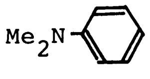


Fig. 2. Reaction of dimedone with *p*-diethylaminobenzenediazonium tetrafluoroborate in the water/1,2-dichloroethane at 15 °C: $ArN_2^+BF_4^-$ 1.0×10^{-4} mol dm^{-3}; substrate 6.0×10^{-3} mol dm^{-3}.
1) In water; 2) 300 rpm; 3) 400 rpm; 4) 500 rpm; 5) 700 rpm; 2′) 300 rpm; $Bu_4N^+Br^-$ 8.0×10^{-3} mol dm^{-3}; 4′) 500 rpm; $Bu_4N^+Br^-$ 6.5×10^{-4} mol dm^{-3}.

From these results, it was expected that the same reaction would be accelerated under appropriate conditions in synthetically more useful liquid–liquid systems. Figure 2 shows a typical rate profile for the reaction of **5** with **6** in the water–1,2-dichloroethane system. It can be seen that the reaction is remarkably accelerated in the two-phase system, even in the absence of a catalyst. Also, the stirring speed is quite important. These results may be understandable by postulating that when a part of both reactants, **5′** and **6**, transfer into an organic phase, the reaction immediately takes place. In contrast, when benzene or cyclohexane was employed as an organic phase, no appreciable acceleration in rate was observed, presumably because both reactants were essentially insoluble in the organic phase. The addition of quaternary onium salts,[17] which are common PTCs for reactions involving carbanion, accelerated the reaction (as illustrated in the case of tetrabutylammonium bromide). It has been expected that the combined use of PTCs for both reactants, i.e., diazonium ion and carbanion, might be effective in the present system. However, no pronounced catalysis was observed; e.g., the addition of tetrabutylammonium bromide and sodium 1-naphthalenesulfonate showed only a slight acceleration compared to a reaction when the former was employed alone. This result may be understandable since the catalytic activities of both PTCs should be decreased owing to a mutual interaction.

Synthesis of Azo Compounds. The usefulness of the present two-phase system was examined in the preparative scale by using various substrates, including particularly unreactive coupling components in

Table 3. Preparation of Azo-compounds

Run	Substrate	Substituent in Ar–N_2^+	Solvent	Condition		Yield[a]/%
				PTC/mol%	Time/h	
1	Dimedone	*p*-NEt_2	H_2O	—	5	5
2			H_2O	—	120	40
3			H_2O-DCE[b]	TBAB[c] (1)	0.7	72
4			H_2O-DCE	TBAB (10)	0.5	90
5		*p*-NEt_2	H_2O	—	27	22
6			H_2O-$CHCl_3$	TBAB (5)	3	64
7		*p*-Cl	H_2O	—	2	—[d]
8			H_2O-DCE	TBAB (10)	1	40
9		*p*-OMe	H_2O	—	10	—[d]
10			H_2O-$CHCl_3$	TBAB (10)	10	43
11		*p*-OMe	H_2O-DCE	$NaClO_4$ (10)	2	70
12			H_2O-DCE	Picric acid (5)	0.7	76

a) Isolated yield of azo compound. b) 1,2-Dichloroethane. c) Tetrabutylammonium bromide. d) Not isolated.

the conventional aqueous system (Table 3). In the case of *p*-toluenesulfonanilide (Run 7), its reactive form is considered to be an anion resulting from the ionization of the N-H bond.[18] The reaction was conducted by using an equimolar amount of a substrate. After the consumption of a diazonium ion was confirmed (except Run 1) through a test with 4-amino-5-hydroxy-2,7-naphthalenedisulfonic acid, resulting azo compounds were isolated by the usual work-up procedure. In contrast to the reaction in an aqueous solution in which the decomposition of the diazonium ion was the major reaction, it can be seen that the present PTC system is very useful for preparing azo compounds.

Experimental

Materials Arenediazonium tetrafluoroborates were prepared by using a general procedure.[19] The crude salt was washed with diethyl ether, dissolved in a minimum amount of acetonitrile, precipitated by adding diethyl ether, and then dried over diphosphorus pentaoxide in vacuo: **2** mp 143—144 °C (decomp); **6** mp 112—113 °C (decomp). Potassium 5,5-dimethyl-1,3-cyclohexanedionide was prepared by adding an equivalent of potassium hydroxide into a methanolic solution of **5**; the solvent was removed and the resulting residue was dried over silica gel. The other materials were obtained from commercial sources, and standardized before use.

Rate Measurements in Homogeneous Systems. The rates in homogeneous solution were measured by using a previously described procedure.[14] The solution (ca. 1×10^{-4} mol dm^{-3}) of a diazonium salt in chlorinated hydrocarbons was prepared as follows: a suspension of diazonium salt (6—7 mg) in a solvent (25 ml) was shaken vigorously for 10 min; then, the residual salt (if present) was filtered off. The fast reactions (Runs 3—11, Table 2) were followed by a stopped-flow technique on a Union Giken RA-1300 instrument.

Rate Measurements in Two-Phase Systems. A mixture of water (25 ml), buffered with sodium carbonate and sodium borate (1×10^{-2} mol dm^{-3} each) at ca. pH 9.5, and 1,2-dichloroethane (30 ml) containing a substrate and a PTC was stirred in a vessel thermostated at the prescribed temperature. After an aqueous solution (5 ml 6×10^{-3} mol dm^{-3}) of the diazonium salt was further added, the mixture was stirred with a flat-bladed mechanical stirrer rotating at a constant speed. At a definite time stirring was stopped and a portion was taken out from the organic phase and diluted with the same solvent to a definite volume. The absorbance due to any azo compound formed was then measured with a Hitachi Model 200-10 spectrometer.

Preparation of Azo Compounds. Into a flask with a mechanical stirrer was added water (100 ml), 1,2-dichloroethane (100 ml), dimedone (2.00 g, 14.3 mmol), sodium carbonate (2.32 g, 21.8 mmol), tetrabutylammonium bromide (0.46 g, 1.4 mmol), and finally *p*-diethylaminobenzenediazonium tetrafluoroborate (3.76 g, 14.3 mmol). The mixture was stirred vigorously for 30 min at 0—5 °C. The organic layer was separated, washed with water, dried over $MgSO_4$, and then evaporated. The residue was recrystallized from benzene–ligroin (1:1) to give 2-(4-diethylaminophenylhydrazono)-5,5-dimethyl-1,3-cyclohexanedione (**7**): mp 128—129 °C; MS, *m/z* 315 (M^+); UV ($ClCH_2CH_2Cl$) 490 nm (ε 22100). Anal. ($C_{18}H_{25}N_3O_2$) C, H, N.

The other azo compounds listed in Table 3 were obtained in a similar manner except that, in the cases of Runs 5, 8, and 10, the crude products were purified on a silica-gel column with benzene.

2-(4-Diethylaminophenylhydrazono)-4,4,4-trifluoro-1-(2-thienyl)-1,3-butanedione: Mp 161—162 °C; MS *m/z* 397 (M^+). Anal. ($C_{18}H_{18}O_2N_3SF_3$) C,H,N.

N-[4-(4-Chlorophenylazo)phenyl]-*p*-toluenesulfonamide: Mp 185—186 °C; MS, *m/z* 385 (M^+). Anal. ($C_{19}H_{16}N_3O_2SCl$) C, H, N.

2-(4-Methoxyphenylazo)-4-nitrophenol: Mp 188—189 °C; MS, *m/z* 241 (M^+). Anal. ($C_{13}H_{11}N_3O_2$) C, H, N.

4-(4-Methoxyphenylazo)-*N,N*-dimethylaniline: Mp 159—160 °C (lit,[20] 161—163 °C); UV ($ClCH_2CH_2Cl$) 410 nm (ε 31400).

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References

1) a) C. M. Starks and C. Liotta, "Phase Transfer Catalysis," Academic Press, New York (1978); b) E. V. Demlow and S. S. Demlow, "Phase Transfer Catalysis," Verlag Chemie, Weinheim (1980); C) W. P. Weber and G. W. Gokel, "Phase Transfer Catalysis in Organic Synthesis," Springer Verlag, Berlin (1977); d) F. Montanari, D. Landini, and F. Rolla, "Phase-transfer Catalyzed Reactions," in "Topics in Current Chemistry," ed by F. L. Boschke, Springer Verlag (1981), Vol. 101, p. 147.

2) A. R. Butler and P. T. Shepherd, *J. Chem. Res. (S)*, **1978**, 339.

3) S. H. Korzeniowski and G. W. Gokel, *Tetrahedron Lett.*, **1977**, 1637.

4) H. Iwamoto, M. Yoshimura, T. Sonoda, and H. Kobayashi, *Bull. Chem. Soc. Jpn.*, **56**, 796 (1983).

5) S. Tamagaki, K. Suzuki, and W. Tagaki, *Chem. Lett.*, **1982**, 1237.

6) M. Ellwood, J. Griffiths, and P. Gregory, *J. Chem. Soc., Chem. Commun.*, **1980**, 181.

7) M. Poindexter and B. McKay, *J. Org. Chem.*, **37**, 1674 (1972).

8) I. Szele and H. Zollinger, "Azo-coupling Reaction, Structures and Mechanism," in "Topics in Current Chemistry," ed by F. L. Boschke, Springer Verlag (1983), Vol. 112, p. 1.

9) O. Dimroth, H. Leichtlin, and O. Friedmann, *Chem. Ber.*, **50**, 1534 (1917).

10) P. N. Juri and R. A. Bartsch, *J. Org. Chem.*, **45**, 2028 (1980).

11) B. Gloor and H. Zollinger, *Helv. Chim. Acta*, **54**, 553 (1971).

12) Ref. 1a, p. 16, 1b, p. 13, and references cited therein.

13) P. R. Singh and R. Kumer, *Aust. J. Chem.*, **25**, 2133 (1972).

14) Y. Hashida, M. Kobayashi, and K. Matsui, *Bull. Chem. Soc. Jpn.*, **44**, 2506 (1971).

15) J. R. Penton and H. Zollinger, *Helv. Chim. Acta,* **54,** 573 (1971).

16) W. A. Sheppard, G. W. Gokel, D. W. Webster, K. Betterton, and J. W. Timberlake, *J. Org. Chem.,* **44,** 1717 (1979); R. A. Bartsch, H. Chen, N. F. Haddock, and P. N. Juri, *J. Am. Chem. Soc.,* **98,** 6753 (1976).

17) The catalytic activities of tetraalkyl onium salts examined were in the following order: $(C_4H_9)_4N^+Br^- \approx (C_4H_9)_4P^+Cl^- > (C_8H_{17})_3N^+C_4H_9Br^- > (CH_3)_4N^+Br^- > (C_8H_{17})_4N^+Br^-$.

18) Ref. 8, p. 32.

19) R. A. Cox and J. Kumamoto, *J. Org. Chem.,* **30,** 4254 (1965).

20) D. Vorländer and E. Wolferts, *Chem. Ber.,* **56,** 1237 (1923).