TABLE I

REPRESENTATIVE REDUCTIVE METHYLATIONS WITH FORMALDEHYDE–$NaBH_3CN$ IN ACETONITRILE AT 25°

Entry	Compd[a]	Time, hr	Registry no.	Product	Yield, %	Product (deriv) mp, °C[b]
1	Cyclohexylamine	2	34201-87-1	*N*,*N*-Dimethylcyclohexylamine	84	(178–180)[c]
2	2-Heptylamine	2	34224-22-1	*N*,*N*-Dimethyl-2-heptylamine	82	(140–142)[d]
3	*endo*-Norbornylamine	2	34287-03-1	*endo*-*N*,*N*-Dimethylnorbornylamine	75	(218–219)[c]
4	*N*-Isopropylcyclohexylamine	2	34224-23-2	*N*-Methyl-*N*-isopropylcyclohexylamine	87	(123–124)[c]
5	α-Methylbenzylamine	2	3160-90-5	*N*,*N*-Dimethyl-α-methylbenzylamine	81	(139–140)[c]
6	*N*-Ethylbenzylamine	1	34224-25-4	*N*-Methyl-*N*-ethylbenzylamine	85	(113–114)[c]
7	Aniline	2	2554-80-5	*N*,*N*-Dimethylaniline	92	(162–163)[c]
8	*p*-Phenetidine	1	34201-88-2	*N*,*N*-Dimethyl-*p*-phenetidine	85	(138–139)[c]
9	*N*-Propylaniline	2	34201-89-3	*N*-Methyl-*N*-propylaniline	83	(111–112)[c]
10	*m*-Chloroaniline	3	34201-90-6	*N*,*N*-Dimethyl-*m*-chloroaniline	86	(143–144)[c]
11	*p*-Bromoaniline	1	586-77-6	*N*,*N*-Dimethyl-*p*-bromoaniline	87	56–57
12	*m*-Nitroaniline	2.5	619-31-8	*N*,*N*-Dimethyl-*m*-nitroaniline	68	56–58
			100-23-2	*N*,*N*-Dimethyl-*p*-nitroaniline	46	162–163
13	*p*-Nitroaniline	5		+		
			100-15-2	*N*-Methyl-*p*-nitroaniline	18	148–150

[a] Ratio of amine:formaldehyde:$NaBH_3CN$: entries 1–9, 1:5:1.6; entries 10–12, 1:10:3; entry 13, 1:20:6. [b] All values are in accord with published values where known; satisfactory elemental analyses were obtained for unknown derivatives. [c] Picrate. [d] Hydrochloride.

Reaction of an aliphatic or aromatic amine with aqueous formaldehyde and $NaBH_3CN$ in methanol (our previously reported[4] conditions for reductive amination) afforded a mixture of starting material and partially methylated products. Presumably the formaldehyde is tied up as the hemiacetal in the methanol system, rendering it less reactive in imine formation. A survey of aprotic solvents which were capable of solubilizing $NaBH_3CN$ was undertaken; acetonitrile proved to be the solvent of choice. The results are summarized in Table I.

This procedure is general for a wide variety of aliphatic and aromatic amines. Amines ranging in basicity from pK_a 10.66 (cyclohexylamine) to 2.47 (*m*-nitroaniline) were successfully methylated under these conditions. Even the very weak base *p*-nitroaniline (pK_a 1.00) was converted to a mixture of mono- and dimethylated products (entry 13). Steric hindrance seems to pose no problem; the hindered amine *N*-isopropylcyclohexylamine (entry 4) underwent methylation without difficulty. Because of the mild conditions, the ease of experimental manipulation, and the high yields of pure products, this reaction appears to be the method of choice for reductive methylation of amines.

Experimental Section

Reductive Methylation of "Reactive" Amines (pK_a > 4).—The preparation of *N*-methyl-*N*-ethylbenzylamine is typical. To a stirred solution of 675 mg (5 mmol) of *N*-ethylbenzylamine and 2 ml (25 mmol) of 37% aqueous formaldehyde in 15 ml of acetonitrile was added 500 mg (8 mmol) of sodium cyanoborohydride.[5] A vigorous exothermic reaction ensued, and a dark residue separated. The reaction mixture was stirred for 15 min, and then glacial acetic acid was added dropwise until the solution tested neutral on wet pH paper. Stirring was continued for an additional 45 min, glacial acetic acid being added occasionally to maintain the pH near neutrality. The solvent was evaporated at reduced pressure, and 20 ml of 2 *N* KOH was added to the residue. The resulting mixture was extracted with three 20-ml portions of ether. The combined ether extracts were washed with 20 ml of 0.5 *N* KOH and then extracted with three 10-ml portions of 1 *N* HCl. The acid extracts were combined and neutralized with solid KOH and then extracted with three 20-ml portions of ether. The combined ether extracts were dried (K_2CO_3) and evaporated *in vacuo* to give 735 mg (98%) of *N*-methyl-*N*-ethylbenzylamine as a colorless, glpc-pure oil. Reaction with 1.5 g of picric acid in ethanol afforded 1.61 g (85%) of picrate, mp 110–112°. One recrystallization from ethanol gave an analytical sample, mp 113–114°.

Anal. Calcd for $C_{16}H_{18}N_4O_7$: C, 50.79; H, 4.80; N, 14.81. Found: C, 51.00; H, 4.79; N, 14.79.

Reductive Methylation of "Unreactive" Amines (pK_a < 4).—The preparation of *N*,*N*-dimethyl-*m*-nitroaniline is typical. To a stirred solution of 690 mg (5 mmol) of *m*-nitroaniline and 4 ml (50 mmol) of 37% aqueous formaldehyde in 20 ml of acetonitrile was added 950 mg (15 mmol) of sodium cyanoborohydride. Glacial acetic acid (0.5 ml) was added over 10 min, and the reaction was stirred at room temperature for 2 hr. An additional 0.5 ml of glacial acetic acid was added, and stirring was continued for 30 min more. The reaction mixture was poured into 75 ml of ether and then washed with three 20-ml portions of 1 *N* KOH and one 20-ml portion of brine. The ether solution was dried (K_2CO_3) and evaporated *in vacuo* to give 840 mg of crude product as a semisolid. Thin layer chromatographic analysis (alumina, benzene) showed one major spot corresponding to the desired product and a trace of monomethylated material. Crystallization from aqueous ethanol afforded 565 mg (68%) of *N*,*N*-dimethyl-*m*-nitroaniline as an orange solid, mp 56–58° (lit.[6] mp 60°), homogeneous on tlc.

Acknowledgment.—Acknowledgment is made to the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

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(5) Available from Alfa Inorganics, Inc.

(6) "Dictionary of Organic Compounds," Oxford University Press, Cambridge, 1965, p 1190.

Kinetics of Azo Dye Formation. Micellar Effects

MARK POINDEXTER[1] AND BRUCE MCKAY*

Department of Chemistry, Harvey Mudd College, Claremont, California 91711

Received September 14, 1971

Few references appear in the literature concerning the effects of micelle-forming surfactants on electrophilic

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(1) National Science Foundation Undergraduate Research Participant, 1971.

aromatic substitution reactions.[2] These reactions are in the main available only in nonaqueous solvents, and micellar studies are not far advanced in other than water solvent. Nevertheless, at least one reaction class of interest for both mechanistic and synthetic reasons is amenable to aqueous solution study. We refer to the formation of azo dyes through coupling of aryldiazonium ions to naphthylamines and naphthols, particularly. Kinetic investigations of these reactions have been initiated and we wish to report some preliminary results.

As a representative reaction we chose the couplings of *p*-nitrobenzenediazonium ion with R salt (2-naphthol-3,6-disulfonate) and S salt (2-naphthol-6-sulfonate).[3] Effects of cationic (CTAB), anionic (NaLS), and nonionic (Triton X-100) surfactants on the coupling rates have been determined.[4] Table I displays our results in the form of rate constant ratios (rate in surfactant solution/rate in absence of surfactant). Coupling rates were determined at a single temperature (26.0°) in acetate-buffered solutions (pH 4.59) and with potassium chloride added to maintain ionic strength, except for solutions containing NaLS. These latter solutions were inhomogeneous if potassium chloride was present, owing to insolubility of the surfactant. The chloride salt was omitted. Basal rates (no surfactant) were variable, within narrow limits, but all rates were reproducible.

TABLE I

FIRST-ORDER RATE CONSTANT RATIOS. COUPLING OF *p*-NITROPHENYLDIAZONIUM ION WITH NAPHTHOLS

	S salt, k/k_0[c]	R salt, k/k_0[c]
[CTAB][a]		
0.001	0.695	0.732
0.002	0.471	0.380
0.003	0.427	
0.005		0.0705
0.010	0.321	
0.20	0.318	0.0556
[NaLS][a]		
0.002	0.556	
0.004	0.221	
0.010	0.124	
0.020	0.0655	
[Triton X-100][b]		
1.0	0.692	0.828
3.0	0.540	0.786
5.0	0.518[d]	0.759[d]

[a] Molar concentration. [b] Concentration in volume per cent. [c] Rate constant in surfactant solution/rate constant in absence of surfactant. [d] Rate ratio is depressed little more in 10% Triton solution.

Inclusion of a surfactant of each charge type (cationic, anionic, nonionic) in the coupling medium results in a depression of the rate constant associated with azo dye formation. As the present system was designed only for demonstration of the susceptibility of a typical coupling to the presence of micelles, a number of features inhibit detailed interpretation of results. For example, increases in pK_a of phenols and naphthols have been found when these substrates are associated with micelles of Triton X-100.[5] Thus, we are unable at present to distinguish rate effects due to naphtholate ion concentration changes from other factors, for both uncharged and ionic detergent systems.

In the absence of requisite physical property data we would only suggest that the results of this study are at least consistent with more general observations regarding the activity of micellar species. In particular, electrostatic repulsions and attractions often appear to be dominating factors influencing reactions of charged species in the presence of micelles.[2,6] If both naphtholate and diazonium ions associate with micelles of the opposite charge type the electrostatic argument becomes more tenable.[6]

A consideration in undertaking this preliminary study was that substrate structures and charges in coupling reactions are variable over a rather wide range, and this feature might be advantageous for elucidating general aspects of micellar catalysis. We intend to make use of structure–charge variations in extending our investigations. Zollinger has shown that coupling of a charged naphthylamine with aryldiazonium ions bearing net formal charges of +1, 0, and −1 obeys, quantitatively, Debye–Hückel salt effect theory.[7] Use of Zollinger's substrates in the presence of micelles should prove very useful in determining how charge–charge interactions in couplings are affected by micelles.

Experimental Section

Standard, published procedures were followed for recrystallizations of cetyltrimethylammonium bromide,[8] sodium lauryl sulfate,[8] sodium 2-naphthol-6-sulfonate,[3] and *p*-nitrobenzenediazonium fluoroborate.[9] Both Triton X-100 and disodium 2-naphthol-3,6-disulfonate were used as received from their suppliers.

Stock solutions were prepared and kinetic data were obtained following the procedures of Cox and Kumamoto.[3] All solutions were maintained at pH 4.59 with 0.01 *M* acetic acid–0.01 *M* sodium acetate. Ionic strength for each solution was kept at 0.22 by addition of potassium chloride, except for solutions containing NaLS (see text).

In a typical experiment 8.7 ml of stock acetate buffer, containing potassium chloride, was mixed with 1.0 ml of 0.012 *M* naphthol solution, also acetate buffered. To the mixed solutions 0.3 ml of diazonium salt solution, buffered, was added. The concentration of diazonium ion was such that the infinite absorbance reading for each run was about 1.0. An aliquot of this solution was placed in a cuvette and this was inserted into the thermostated cell compartment of a Cary 13 recording spectrophotometer. The increase in absorbance at 485–490 nm, λ_{max} for the dyes, was measured as a function of time. Pseudo-first-order rate constants were calculated from plots of $\log (A_\infty - A_t)$ *vs.* t.

Reaction temperatures were 26.0 ± 0.3°. Rate constants were reproduced to at least ±4%. Generally, the higher the detergent concentration the better the rate constant reproduction, since the reaction half-life becomes very short (*ca.* 1 min or less) as the detergent concentration approaches zero.

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[2] A recent comprehensive review of micellar catalysis contains only one such example: coupling of halonaphthols with quinionediimenes. E. J. Fendler and J. H. Fendler, *Advan. Phys. Org. Chem.*, **8**, 271 (1970).

[3] R. J. Cox and J. Kumamoto, *J. Org. Chem.*, **30**, 4254 (1965).

[4] CTAB = cetyltrimethylammonium bromide; NaLS = sodium lauryl sulfate.

[5] L. K. J. Tong and M. C. Glesman, *J. Amer. Chem. Soc.*, **79**, 4305 (1957).

[6] A more fully developed argument applicable to our results is to be found in a recent report of micellar effects on Meisenheimer complex equilibria: J. H. Fendler, E. J. Fendler, and M. V. Merritt, *J. Org. Chem.*, **36**, 2172 (1971).

[7] H. Zollinger, *Helv. Chim. Acta*, **36**, 1723 (1953).

[8] E. F. J. Dunstee and E. Grunwald, *J. Amer. Chem. Soc.*, **81**, 4540 (1959).

[9] E. B. Starkey, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 225.

Solutions containing ionic detergents were made up by adding the desired weight of the solid to the stock solutions just before mixing with diazonium salt solutions. No volume change effects were observable. Because of the larger quantities of Triton X-100 needed this detergent was added to the stock acetate buffer before the final dilution to the mark with water.

Registry No.—*p*-Nitrophenyldiazonium ion, 14368-49-1; S salt, 93-01-6; R salt, 148-75-4.

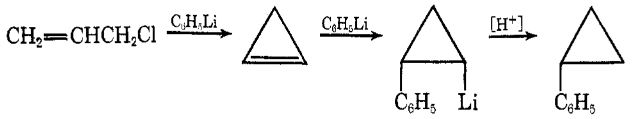
The Reaction of Phenyllithium with Allyl Chloride. Addition of Phenyllithium to Lithiated Cyclopropenes

DOUGLAS E. APPLEQUIST* AND EDWARD G. SAURBORN

Department of Chemistry, University of Illinois, Urbana, Illinois 61801

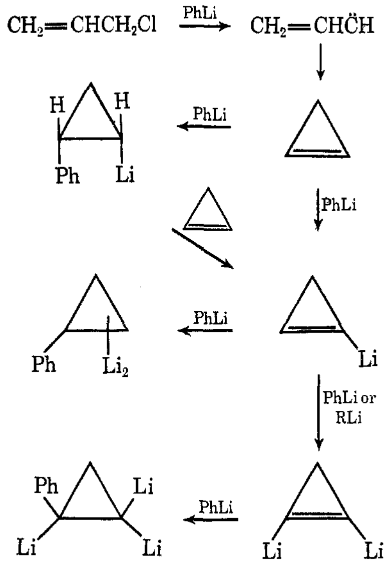
Received October 26, 1971

The formation of phenylcyclopropane from the reaction of phenyllithium with allyl chloride in ether has been the subject of at least four proposed mechanisms.[1,2] The mechanism which has gained the most impressive confirmation[3] is 1,1 elimination to form cyclopropene, followed by addition of phenyllithium to the double bond and protolysis of the 2-phenylcyclopropyllithium thus formed. The principal difficulty with this mechanism is that the source of the proton in the last step has not been found. It has been reported by two groups[2,3] that, if reaction mixtures were treated with deuterium oxide, the phenylcyclopropane isolated contained no deuterium, apparently ruling out water in the isolation procedure as the proton source. Magid[3] has suggested ether, allylbenzene, and allyl chloride as proton sources, but the first two are too slow in their reactions with phenylcyclopropyllithium[3] to account for the lack of deuterium incorporation with D_2O after a reaction run under mild conditions,[2] and the last is unsuitable under at least some conditions since allyl-1,1-d_2 chloride gives phenylcyclopropane containing only one deuterium[3] (confirmed in this work).



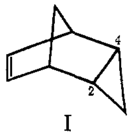
The source of the proton for the last step and hence a strong confirmation of the cyclopropene mechanism has now been found to be cyclopropene itself. If the reaction is run with a 1.50 mole ratio of phenyllithium to allyl chloride (as opposed to ratios 0.75–1.20 previously used), followed by a deuterium oxide quench, the isolated phenylcyclopropane contains an average deuterium content of 1.47 atoms (combustion analysis) and includes d_1, d_2, and d_3 species (mass spectrometry). The deuterium atoms were shown to be exclusively on the cyclopropane ring by quantitative integration of the H nmr and D nmr spectra, with 0.37 atoms in the α position and 1.10 atoms in the β positions. A control showed that treatment of phenylcyclopropane with phenyllithium, followed by a deuterium oxide quench, gave no detectable deuterium incorporation. It is concluded that phenylcyclopropane does in fact arise from addition of phenyllithium to cyclopropene, and that di- and trideuterated phenylcyclopropanes form as a result of addition of phenyllithium to the metalated cyclopropenes, 1-lithiocyclopropene and 1,2-dilithiocyclopropene (Scheme I).

SCHEME I



The source of protons to make phenylcyclopropane in the absence of sufficient phenyllithium is then seen to be cyclopropene, certainly the best proton acid in the medium.

Two other observations serve to confirm the mechanism shown in Scheme I. The first is that, when a reaction mixture of allyl chloride and methyllithium was quenched with deuterium oxide and the resulting cyclopropene was allowed to react with cyclopentadiene, the adduct I was obtained with 1.48 atoms/molecule of deuterium, all of it being in the 2 and 4 positions, according to H nmr and D nmr spectra, in which the multiplet at δ 1.31 was assigned to C_2 and C_4. The presence of 1,2-dilithiocyclopropene in a reaction mixture very similar to the phenyllithium mixture was thus supported, although the experiment did not exclude the possibility of base-catalyzed exchange of unlithiated or monolithiated cyclopropene with deuterium oxide.



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A second observation pertinent to the mechanism in Scheme I is the finding that 3-phenyl-1,5-hexadiene (II) is a minor (2–5%) product of the reaction of phenyllithium with allyl chloride. When the reaction was run with allyl-1,1-d_2 chloride, the II formed contained almost no proton at C_3, while positions C_4 and C_6

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[1] S. Wawzonek, B. Studnicka, H. J. Bluhm, and R. E. Kallio, *J. Amer. Chem. Soc.*, **87**, 2069 (1965).

[2] D. E. Applequist and M. A. Lintner, *J. Org. Chem.*, **31**, 3062 (1966).

[3] R. M. Magid and J. G. Welch, *J. Amer. Chem. Soc.*, **90**, 5211 (1968), and earlier references cited therein.