Reductive Dehalogenation of Aryl Chlorides by Alkali Metals and Sodium Naphthalenide. Evidence for Radical Intermediates

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On treatment with sodium or sodium naphthalenide (NaNp), aryl halides undergo reductive dehalogenation. When the aryl halide is *N*-(*o*-chlorobenzal)aniline (1), a molecule of the ether solvent is observed to add to the imine group during the reductive dehalogenation. This reaction is used here as a probe to determine the mechanism whereby the hydrogen atom is abstracted from the solvent. With isopropyl methyl ether as the solvent, attack occurs preferentially on the α H of the isopropyl group. This reaction is most plausibly explained by the aryl radical (generated by the loss of chloride ion from the radical anion of 1) abstracting the proton before it is reduced to an aryl anion. This same behavior is observed when NaNp is used as the dehalogenating agent.

In our earlier examination[1] of the reductive dehalogenation of *N*-(*o*-chlorobenzal)aniline (**1**) by alkali metals, the capture of solvent-derived reactive intermediates was observed (eq 6). The mechanism for the reaction can be formulated as eq 1, 2, 3, and 6 or 1, 4, 5, and 6, the chief distinction being whether or not the aryl radical formed in the initial reduction of **1** (ArCl, eq 1) abstracts a hydrogen from the solvent (HS) faster than it is reduced to an aryl anion. In the case of alkyl radicals generated by strong reducing agents, extremely rapid reductions have been detected,[2] but opposing views have been expressed for aryl radicals.[3]

$$\mathrm{ArCl} \xrightarrow{e} \mathrm{Ar}\cdot + \mathrm{Cl}^- \tag{1}$$

$$\mathrm{Ar}\cdot + \mathrm{HS} \longrightarrow \mathrm{ArH} + \mathrm{S}\cdot \tag{2}$$

$$\mathrm{S}\cdot \xrightarrow{e} \mathrm{S}^- \tag{3}$$

$$\mathrm{Ar}\cdot \xrightarrow{e} \mathrm{Ar}^- \tag{4}$$

$$\mathrm{Ar}^- + \mathrm{HS} \longrightarrow \mathrm{ArH} + \mathrm{S}^- \tag{5}$$

$$\mathrm{ArCl(or\ ArH)} + \mathrm{S}^- \longrightarrow \mathrm{SArCl}^- \ (\mathrm{or\ SArH}^-) \tag{6}$$

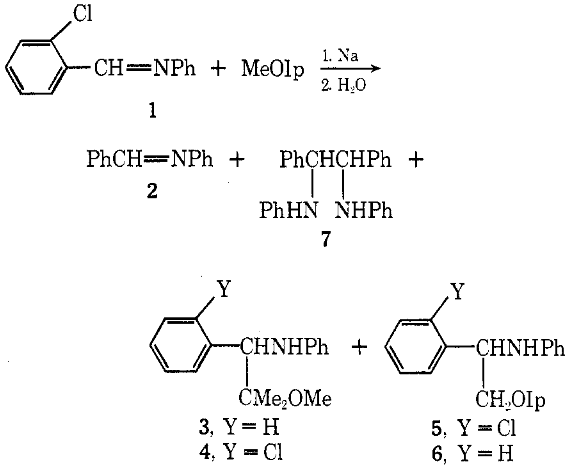
In our initial efforts[1] to use this reaction as a chemical probe and assess the reactive capabilities of the aryl radicals, the competitive behavior of a solvent mixture was examined. However, interpretation was complicated by the basicity differences of the components which can perturb the solvent ratio in the vicinity of the reaction site. The present study avoids this problem by using isopropyl methyl ether (IME) as the solvent. IME was selected since the two alkyl groups contained reactive α hydrogens as far apart on the reactivity scale as possible (primary *vs.* tertiary) and the products formed would not be diastereomeric mixtures as was the case in the earlier study.[1]

The reaction between **1** and sodium proceeded rapidly in IME at room temperature and was essentially complete in 4 hr. Examination of the reaction product by gas chromatography (vpc) disclosed four peaks. The second peak proved to be **1** and the first its dechlorinated analog *N*-benzalaniline (**2**). The remaining two were isolated by preparative vpc. Analytical and spectral data established that the third peak was *N*,1-diphenyl-2-methoxy-2-methylpropylamine (**3**). The fourth peak was a mixture of two compounds and complete resolution could not be achieved by vpc. Column chromatography provided the major component which was identified as 1-(*o*-chlorophenyl)-2-methoxy-2-methyl-*N*-phenylpropylamine (**4**).

The second component of this mixture was the isomeric compound 1-(*o*-chlorophenyl)-2-isopropoxy-*N*-phenylethylamine (**5**). This identification was based on a comparison of the spectral properties of **4** with those of the mixture of **4** and **5**.

The mass spectrum of the mixture showed small but characteristic peaks at $\mathrm{M}^+ - \mathrm{OCH}_3$ and $\mathrm{M}^+ - \mathrm{OIp}$ while that of **4** showed only the former. The nmr spectrum of the mixture also supported the presence of **5**. The existence of **6** was indicated by an $\mathrm{M}^+ - \mathrm{OIp}$ peak in the mass spectrum[4] of the vpc peak corresponding to **3** but supportive evidence (nmr or vpc resolution) could not be obtained because of the small quantities involved.

The dimeric diamines **7** were also detected in the reaction product by their characteristic benzylic proton absorption in the nmr spectrum. Thus the overall reaction was quite analogous to that observed with diethyl ether and tetrahydrofuran, *i.e.*, eq 7. The possibility of reductive dechlorination proceeding in the reaction products (*e.g.* **4** → **3**) can be ruled out by the fact that the product composition remained unchanged once the reaction was complete (see Table I, Experimental section). This is not surprising since



(7)

OIp = isopropoxy

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[1] J. G. Smith and I. Ho, *J. Org. Chem.*, **37**, 4260 (1972).

[2] (a) J. F. Garst, *Accounts Chem. Res.*, **4**, 400 (1971), and references therein; (b) W. Adam and J. Arce, *J. Org. Chem.*, **37**, 507 (1972); (c) S. Bank and J. F. Bank, *Tetrahedron Lett.*, 4581 (1971); (d) W. C. Danen, T. J. Tipton, and D. G. Saunders, *J. Amer. Chem. Soc.*, **93**, 5186 (1971).

[3] (a) G. D. Sargent, *Tetrahedron Lett.*, 3279 (1971); (b) T. C. Cheng, L. Headley, and A. F. Halasa, *J. Amer. Chem. Soc.*, **93**, 1502 (1971).

[4] Determined on a MS-30 vpc–mass spectrometer by J. M. Miller, Department of Chemistry, Brock University, St. Catharines, Ontario.

the products of the reaction are amine anions and further electron transfers from the reducing agent are discouraged.

Discussion

These product analyses establish that the preferred point of attack on IME is the α H of the isopropyl group. The question is whether this reflects attack by an aryl radical or anion. As a general rule, proton abstraction by a radical occurs with a relative reactivity sequence of tertiary > secondary > primary. This sequence holds true for a wide variety of substrates and radicals.[5] In contrast, the sequence is reversed, *i.e.*, primary > secondary > tertiary, if the attacking species is an anion.[6,7]

Thus it appears that the products observed can be attributed to a radical attack upon the solvent (*i.e.*, reaction 2) although a minor contribution involving anionic attack *via* reactions 4 and 5 cannot be excluded. Indeed, the relative reactivity per hydrogen of primary *vs.* tertiary protons in IME is approximately[8] 1:6, a value similar to that observed[5] for hydrogen abstraction by a variety of radicals.

The possibility that the primary α's of the solvent are actually removed more rapidly than the tertiary but, because of a slower rate of addition of the primary solvent-derived intermediate to the imine, the tertiary solvent-derived intermediate predominates in the product can be countered by the following. Whatever the nature of the solvent-derived intermediates, the amount initially formed equals the moles of organic chlorine lost in the reduction. This amount can be calculated from the product analysis;[9] the difference between this value and the amount of the solvent-derived intermediates[10] appearing in the products represents those intermediates which are not captured but decompose. *Assuming all such intermediates* are formed by attack at the primary α H's of IME, then attack occurs equally at the methyl and isopropyl groups of the solvent. The relative reactivity (per H) is reduced from the observed tertiary:primary = 6:1 to 3:1. Thus, even on this assumption, the results favor an interpretation based upon radical attack on the solvent.

Supporting evidence for deprotonation of the solvent by aryl radicals was obtained with a trapping reagent. The dechlorination of **1** was effected by sodium in a mixed tetrahydrofuran–cumene solvent. Bicumyl was detected in small amounts among the reaction products. Suitable control experiments demonstrated that the bicumyl arose as a consequence of the dechlorination of **1**.

The behavior described here contrasts with the conclusion of Garst[2a] and of Sargent[3a] who, on the basis of excellent supportive evidence, deduced that the radicals formed on dehalogenation are largely reduced to anions prior to any other reaction. However, it is possible that, *under the reaction conditions employed here*, the intermediate radical anion formed from **1** and sodium might not collapse to chloride ion and aryl radical until it had diffused to a region remote from the sodium. Protonation of the radical would then occur prior to further reduction.

By using sodium naphthalenide as the reducing agent, the physical limitations just described can be eliminated. Since NaNp would not form in IME at room, temperature this was done[11] at −78° using a 2 :1, 3:1 and 4:1 ratio of naphthalene to **1**. The composition of products from the first reaction corresponded closely to those obtained in the incomplete (2 hr) reaction with sodium. In the case of the last reaction, both the nmr spectrum and the vpc analysis showed an increase in the amount of **3** relative to **4** and **5** but the ratio of the last two compounds did not change significantly from that observed in the reactions with sodium.

However, in none of these reactions was excess NaNp present. This is indicated by the position of the equilibrium between NaNp and the hydrocarbon, by the presence of **1** and the lack of any dimeric diamines **7** in the reaction products. At this moment, it must be concluded that, in the absence of excess NaNp, the reductive dehalogenation of **1** proceeds by the same radical mechanism with both NaNp and sodium. It is further suggested that NaNp and **1** react to produce the radical anion of **1** which is then the effective reducing agent in the reaction under study. It may well be that this reducing agent is not sufficiently reactive to convert the initial formed aryl radical to its corresponding anion.

Throughout the discussion, it has been assumed that the solvent-derived intermediate adding to the imine is an anion. However, bearing in mind the reducing powers of this system, it is possible that the solvent-derived radical may itself add to the unsaturated substrate. We plan to devote further consideration to this problem.

Experimental Section[12]

All operations with the alkali metal compounds were performed under nitrogen which had been scrubbed by a refluxing solution of benzophenone ketyl in xylene. The solvent, isopropyl methyl ether, was prepared in 73% yield by alkylating[13] sodium isopropoxide with dimethyl sulfate. The fraction boiling 31–32° was further purified by distillation from LiAlH$_4$ immediately before use. Cumene was dried by refluxing over sodium and distilled from sodium immediately before use.

General Procedure.—The procedure described[1] earlier was followed. A normal preparative experiment involved 2.16 g

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[5] This has been comprehensively reviewed by G. A. Russell in "Free Radicals," J. K. Kochi, Ed., Wiley, New York, N. Y., 1973, Chapter 7, pp 275–331.

[6] See the discussion by D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapter 1.

[7] Particularly pertinent references involving the reaction of butyllithium with a variety of ethers are (a) R. B. Bates, L. M. Kroposki, and D. E. Potter, *J. Org. Chem.*, **37**, 560 (1972); (b) J. C. Carnahan, Jr., and W. D. Closson, *ibid.*, **37**, 4469 (1972); (c) R. A. Ellison, R. Griffin, and F. N. Kotsonis, *J. Organomet. Chem.*, **36**, 209 (1972).

[8] This assumes that the capture of the solvent-derived fragments by a *single* substrate best approximates the concentration of the reactive intermediates. Thus the ratio of **4** and **5** representing capture by **1** was used in this estimation.

[9] The product analyses of Table I must be converted to equivalents of monomeric units; *i.e.*, the moles of dimer must be doubled.

[10] 65–75% of the intermediates appear in the products.

[11] The equilibrium uptake of sodium in IME was 0.33 g-atom/mol of naphthalene.

[12] Melting points are uncorrected and were determined with a Mel-Temp melting point apparatus. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer and nmr spectra on a Varian T-60 spectrometer and the chemical shifts are reported in δ units. Analytical and preparative vapor phase chromatography (vpc) were performed on a Varian-Aerograph 1520 instrument. Mass spectra were determined on an AEI MS-30 mass spectrometer. Silica gel (70–325 mesh ASTM) from E. Merck AG was used for column chromatography and Eastman chromagram 6060 (silica gel) sheets were used for thin layer chromatography (tlc). Analyses were determined by M-H-W Laboratories, Garden City, Mich.

[13] An adaptation of the procedure reported by J. H. Robson and G. F. Wright, *Can. J. Chem.*, **38**, 21 (1960).

(0.01 mol) of *N*-(*o*-chlorobenzal)aniline (**1**), 50 ± 5 ml of IME, and 0.5 g (0.02 g-atom) of sodium shaken for the chosen time interval. The red-brown solution was drained from the excess metal, cooled to −60°, and quenched by injecting 2 ml of methanol.

The IME was recovered by distillation, the residue was treated with water, and the organic products were isolated by an ether extraction. Evaporation of the ether extracts followed by a 24-hr pumping provided solvent-free product which could be analyzed by nmr (see Table I). Analytical separations by vpc were accomplished using flame ionization detectors, a 5 ft by $^1/_8$ in. column packed with 10% Carbowax 20M on 100–120 mesh Chromosorb W at 195° and a He flow rate of 30–40 ml/min. Spiking with authentic samples was used to characterize the elution peaks.

TABLE I

ANALYSIS OF THE REACTION PRODUCTS

Compd	Using sodium, reaction time, hr					Using NaNp, mole ratio[b]		
	2[a]	4	6	8	24	2	3	4
1	32	tr[c]				36	23	13
2	20	tr[c]				23	20	39
3	3	13	13	13	16	7	29	35
4	27	35	35	34	29	26	20	9
5	10	17	16	17	16	8	8	4
7 (meso)	2	18	18	19	18			
7 (racemic)	2	17	18	17	20			

[a] About 4% of the chlorine-containing dimers analogous to **7** were observed. [b] Mole ratio of naphthalene to **1**; vpc analyses. [c] <1%.

The products from a 24-hr run were separated by preparative vpc using a 10 ft by $^3/_8$ in. column packed with 10% Carbowax 20M on 60–80 mesh Chromosorb W operated at 185° with a He flow rate of 60 ml/min.

The first peak which eluted was identified as *N*-benzalaniline by comparison of its ir and nmr spectra with those of a reference sample. The second peak, **1**, was too small to collect in the 24-hr reactions.

The third peak which eluted was recrystallized from methanol to give **3** as a white solid: mp 96–98°; ir (KBr) 3370, 3060, 2990, 1600, 1500, 1320, 1060, 740, 700, and 690 cm^{-1}; nmr ($CDCl_3$) δ 1.07 (s, 3) and 1.27 (s, 3) ($C\mathbf{H}_3CC\mathbf{H}_3$), 3.20 (s, 3, OCH_3), 4.20 (s, 1, benzylic H), 4.90 (br s, 1, NH, exchanging with D_2O), 6.4–7.5 (m, 10, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 255 (1, M^+), 224 (1, $M^+ - MeO$), 183 (15), 182 (100, $M^+ - C_4H_9O$), 104 (8), 77 (18), 73 (22).

Anal. Calcd for $C_{17}H_{21}NO$: C, 79.95; H, 8.29; N, 5.49. Found: C, 80.22; H, 8.02; N, 5.53.

The fourth peak which eluted was a partially resolved mixture of two compounds. Chromatography on 60 g of silica gel with benzene as eluent provided the major component and recrystallization from methanol gave **4**: mp 87–90°; ir (KBr) 3370, 3060, 2990, 2930, 1600, 1510, 1320, 1050, 730, 700, and 680 cm^{-1}; nmr ($CDCl_3$) δ 1.08 (s, 3), 1.40 (s, 3) ($C\mathbf{H}_3CC\mathbf{H}_3$), 3.27 (s, 3, OCH_3), 4.93 (br s, 2, NH and benzylic H, NH exchanging with D_2O), 6.4–7.7 (m, 9, aromatic H); mass spectrum (70 eV) *m/e* (rel intensity) 291 (0.6, M^+), 289 (1.5, M^+), 260 (0.6, $M^+ - OCH_3$), 258 (1.7, $M^+ - OCH_3$), 218 (33, $M^+ - C_4H_9O$), 217 (14), 216 (100, $M^+ - C_4H_9O$), 77 (28), 73 (82).

Anal. Calcd for $C_{17}H_{20}NClO$: C, 70.46; H, 6.96; N, 4.83; Cl, 12.24. Found: C, 70.51; H, 7.14; N, 4.78; Cl, 12.46.

The mixture of **4** and **5** as originally isolated by preparative vpc had an nmr spectrum resembling **4** with an additional absorption at 1.20 [half of double d, $OCH(C\mathbf{H}_3)_2$] and 3.3–4.0 [m, $C\mathbf{H}_2OCH(CH_3)_2$]; mass spectrum (70 eV) *m/e* (rel intensity) 291 (0.5, M^+), 289 (1.2, M^+), 260 (0.5, $M^+ - OCH_3$), 258 (1.2, $M^+ - OCH_3$), 232 (0.4, $M^+ - OIp$), 230 (1.1, $M^+ - OIp$), 218 (35), $M^+ - C_4H_9O$), 217 (15), 216 (100, $M^+ - C_4H_9O$), 180 (20), 179 (10), 77 (58), 73 (61), 51 (19).

Reaction in Tetrahydrofuran–Cumene Mixed Solvents.—The procedure was the same as that described. The solvent composition was determined by weighing the reaction vessel after each of the components was distilled in. In a typical experiment, 45 g of tetrahydrofuran (THF) and 31 g of cumene were used with a 24-hr reaction time. The quenched reaction mixture was distilled to remove the solvent and the residue analyzed by vpc as described earlier. Bicumyl[14] (1% of the total reaction mixture) eluted earlier than any of the other components and was identified by spiking with an authentic sample. A confirmatory identification was made using a 5 ft by $^1/_8$ in. column packed with 10% UCW-98 on 100–120 mesh Chromosorb W with the same operating conditions.

Control experiments were performed with sodium metal and THF–cumene, both with and without *N*-benzalaniline (**2**). No bicumyl was detected, showing that neither sodium metal alone nor the reductive dimerization of **2** was responsible for the bicumyl observed when **1** was present.

Reductive Dehalogenations with Sodium Naphthalenide.—The sodium naphthalenide was prepared by stirring a mixture of excess sodium, naphthalene (0.01, 0.015, or 0.02 mol), and IME (~40 ml) in a flask equipped with a side arm and stopcock at −78° for 8 hr. The dark green solution was drained from the excess metal through the side arm into a second N_2-filled flask precooled to −78°. The Schiff base **1** (0.005 mol) dissolved in 1–2 ml of IME was injected through a septum into the stirred solution. Rapid decolorization to a light yellow color occurred. The solution was stirred for 8 hr at −78°, then warmed to room temperature, and diluted with water, and the products were isolated by an ether extraction. Analyses were conducted as described except that the vpc column length was increased to 10 ft so as to estimate the ratio of **4** and **5**. This was necessary since the large amount of naphthalene made the nmr analysis unreliable except in the case of the 2/1 reaction. Here the nmr analysis showed **1** (36%), **2** (29%), **3** (5%), **4** (22%), and **5** (8%). None of the nmr spectra showed the presence of **7**.

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Registry No.—**1**, 5877-49-6; **3**, 41203-41-2; **4**, 41203-42-3; **5**, 41203-43-4; sodium naphthalenide, 25398-08-7.

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[14] Reference sample prepared according to C. Walling and R. Rabinowitz, *J. Amer. Chem. Soc.*, **81**, 1137 (1959).