The Cleavage of Diaryl Ethers by Grignard Reagents in the Presence of Cobaltous Chloride. Part I. Monosubstituted Diphenyl Ethers.

By R. L. Huang.

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Fission of 11 monosubstituted diphenyl ethers $R{\cdot}C_6H_4{\cdot}OPh$ by a Grignard reagent in the presence of cobaltous chloride has been studied, and the resulting phenolic mixtures have been analysed. The molar ratios $R{\cdot}C_6H_4{\cdot}OH : PhOH$ obtained are explained in terms of relative stability of the intermediate aryloxy-radicals. The permanent electronic effects of R can thus be evaluated.

Diphenyl ether, although remarkably stable towards the usual ether-hydrolysing reagents (alkalis and Lewis acids), undergoes smooth fission by alkali metals in liquid ammonia, or somewhat less effectively, by Grignard reagents at elevated temperatures (Ungnade, *Chem. Reviews*, 1946, **38**, 405; Spath, *Monatsh.*, 1914, **35**, 319). The former reaction has been well investigated, and shown to proceed *via* intermediate anions (Sowa *et al.*, *J. Amer. Chem. Soc.*, 1937, **59**, 603, 1488; 1938, **60**, 94; cf. Birch, *J.*, 1947, 102); the latter, judged from the reaction conditions and by-products (*e.g.*, *o*-phenylphenol), appears to involve a homolytic process. Kharasch and Huang recently (*J. Org. Chem.*, 1952, **17**, 669) found that, by employing anhydrous cobaltous chloride in conjunction with a Grignard reagent, extensive cleavage of diphenyl ether can be brought about even at room temperature. The reaction in all probability involves free radicals, and atomic hydrogen has been postulated as the active agent. A study of the fission of variously substituted diphenyl ethers $R{\cdot}C_6H_4{\cdot}OPh$ by this method and analysis of the resulting phenolic mixtures ($R{\cdot}C_6H_4{\cdot}OH$ + PhOH) would reveal the effect of the substituent groups on the ether towards fission by free radicals, and thus provide information concerning the electronic effects of such groups. In the present investigation eleven monosubstituted diphenyl ethers have been subjected to the Kharasch–Huang procedure, and the resulting phenolic mixtures analysed.

A fairly wide variety of substituents can be investigated by this method, including groups of varying combinations of moderately strong $\pm I$ and $+M$ effects. However, certain groups are outside its scope, *e.g.*, OH, NH_2, and in particular groups with a $-M$ effect such as NO_2, CO_2H, and CN, since all these are subject to attack by the Grignard reagent. The Grignard reagent–cobaltous chloride combination has been shown (Kharasch and Huang, *loc. cit.*) not to affect an alkyl aryl ether linkage (as in anisole), and so alkoxy-groups can also be studied. In view of the finding that the above combined reagents reduce bromo- and dichloro-benzene to benzene and chlorobenzene, respectively (Kharasch, Sayles, and Fields, *J. Amer. Chem. Soc.*, 1944, **66**, 481), it became necessary to ascertain whether the chlorine atom in a chlorodiphenyl ether was similarly affected. The neutral fractions from the cleavage of *o*- and *p*-chlorophenyl ether yielded no less than 72% and 74%, respectively, of the unchanged chlorodiphenyl ether while diphenyl ether was not formed to any appreciable extent; thus reduction of the chlorine atom, if it occurred at all, could not be a competing reaction.

The Grignard reagent of choice was *n*-butylmagnesium bromide, 4 mols. of which were employed with 2·5 mols. of anhydrous cobaltous chloride for each mol. of ether. The phenols produced were isolated by alkali-extraction and distilled in a partial vacuum. A forerun of approximately 5—6% was discarded, distillation being then continued until practically no residue remained. The main fraction so obtained was analysed. The estimated phenol content was thus slightly low, the maximum error being 5—6% depending on the relative volatility of the substituted phenol present. Derivatives were prepared from both fractions to establish the identity of the components.

The composition of mixtures of phenol and the methoxy- and chloro-phenols was determined by micro-Zeisel and Carius analyses. Mixtures of phenol and the cresols were analysed iodometrically, the method being based on that of Redman, Weith, and Brock (*J. Ind. Eng. Chem.*, 1913, **5**, 831), which is comparatively sensitive to presence of traces of impurities, particularly with *m*-cresol. The boiling points of these mixtures, and the fact that they readily formed pure derivatives of the respective cresols, indicated that these mixtures contained mostly the cresols, in agreement with the titrations. With a slight modification the iodometric method was found applicable to the estimation of the *o*- and *p*-chlorophenol, and the results agreed well with those obtained by microanalyses. *p-tert.*-Butylphenol and *p*-phenylphenol were isolated and weighed as such.

EXPERIMENTAL

Synthesis of Ethers.—Except for *o*-chlorodiphenyl ether, Ullmann and Sponagel's method (*Ber.*, 1905, **38**, 2212), using a phenol and the appropriate aryl bromide, was employed throughout: *o*-, *m*-, and *p*-methyl- and -methoxy-diphenyl ethers (Sowa *et al.*, *locc. cit.*; Lea and Robinson, *J.*, 1926, 411); *m*-chlorodiphenyl ether (from phenol, 22% yield) (Found: Cl, 16·9. Calc. for $C_{12}H_9OCl$: Cl, 17·3%) (cf. Suter and Green, *J. Amer. Chem. Soc.*, 1937, **59**, 2578); *p*-chlorodiphenyl ether (from *p*-chlorophenol, 26%) (Found: Cl, 17·1%) (cf. Brewster and Stevenson, *ibid.*, 1940, **62**, 3144); *p-tert.*-butyldiphenyl ether (from *p-tert.*-butylphenol, 55%) (Found: C, 84·8; H, 8·1. Calc. for $C_{16}H_{18}O$: C, 85·0; H, 8·0%) (cf. Pajeau, *Compt. rend.*, 1944, **218**, 236); and *p*-phenyldiphenyl ether (from phenol, 50%) (cf. Lüttringhaus and Sääf, *Annalen*, 1945, **557**, 25). *o*-Chlorodiphenyl ether was prepared from *o*-aminodiphenyl ether by a Sandmeyer reaction (Brewster and Stevenson, *loc. cit.*).

p-Chlorodiphenyl ether gave, on nitration with sulphuric–nitric acid at *ca.* 10°, a mononitro-derivative, yellow needles (from ethanol), m. p. 150—151° (Found: Cl, 14·2. Calc. for $C_{12}H_8O_3NCl$: Cl, 14·2%).

Cleavage Experiments.—The cleavage of *p*-chlorodiphenyl ether, a typical experiment, is described: *p*-Chlorodiphenyl ether (12 g., 0·06 mole) was added to the Grignard reagent prepared from *n*-butyl bromide (33 g., 0·24 mole) and magnesium (5·8 g., 0·24 mole) in diethyl ether (200 c.c.), and vigorous stirring started. Anhydrous cobaltous chloride (18 g., 0·15 mole) was then added in approx. 30 portions during 2·5 hr., at room temperature (28°). Large volumes of gases were evolved, and the mixture became black. At the end of the addition of cobaltous chloride the mixture was stirred for a further hour, after which it was decomposed and the precipitate brought into solution by the cautious addition of water (*ca.* 75 c.c.) with external cooling, followed by 5N-sulphuric acid (*ca.* 100 c.c.). The organic layer was separated, and the aqueous layer thoroughly extracted with ether (5 × 100 c.c.). The combined extracts were washed once with dilute sulphuric acid (50 c.c.) and evaporated to *ca.* 150 c.c., and the phenols present taken up in 5% aqueous sodium hydroxide (3 × 50 c.c.). The alkali extract was washed twice with ether, acidified with 5N-sulphuric acid, saturated with sodium sulphate, and again extracted with ether (5 × 70 c.c.). After being washed with a little 20% aqueous sodium carbonate (30 c.c.) the ethereal solution was dried ($MgSO_4$) and concentrated to a crude mixture of phenols (2·4 g.) which was then distilled, giving the fractions (i) b. p. 108—114°/38 mm. (0·12 g.) and (ii) b. p. 114—136°/38 mm. (2·1 g.); there was practically no residue. Fraction (i) gave tribromophenol (m. p. and mixed m. p.); fraction (ii) gave *p*-chlorophenyl benzoate and *p*-chlorophenoxyacetic acid. The chlorine content of fraction (ii) (Found: Cl, 22·3, 22·5%) corresponded to 76 moles % of chlorophenol.

The neutral fraction was also concentrated and fractionated, giving fractions: (i) b. p. 50—84°/760 mm. (*ca.* 0·4 g.), apparently a mixture of diethyl ether and benzene; (ii) b. p. 84—102°/760 mm. (0·5 g.), consisting mainly of benzene (1 : 3-dinitro-derivative, m. p. and mixed m. p. 88—90°); (iii) b. p. 93—97°/0·7 mm. (*ca.* 0·2 g.); (iv) b. p. 97—100°/0·7 mm. (1·3 g.), n_D^{25} 1·5798; (v) b. p. 100—101°/0·7 mm. (4·5 g.), n_D^{25} 1·5839; and (vi) a dark viscous residue (1·2 g.). Fraction (v), the main fraction, was *p*-chlorodiphenyl ether (Found: Cl, 17·25%). (Note: diphenyl ether has b. p. 78°/0·7 mm., n_D^{24} 1·5826), as was the greater part of (iv), since the latter on nitration gave the mononitro-derivative of *p*-chlorodiphenyl ether (m. p. 150—151°, alone or mixed with an authentic sample prepared previously.) This brings the recovered *p*-chlorodiphenyl ether to approx. 5·8 g. (74%).

In the case of *o*-chlorodiphenyl ether, 72% of the unchanged ether was recovered as crystalline material.

In a second cleavage experiment with *p*-chlorodiphenyl ether, the phenolic mixture contained 21·7% of chlorine (73 moles % of *p*-chlorophenol; iodometric titration gave 73 moles %).

p-*Phenyldiphenyl Ether.*—The phenols produced by the cleavage of this ether (15·0 g.) were taken up in 5% aqueous potassium hydroxide (200 c.c.) which was then heated to 85° and acidified with 2N-hydrochloric acid. (Note: at 80° a 5% aqueous solution of sodium chloride dissolves 10% by weight of phenol.) The *p*-phenylphenol thus precipitated was filtered, washed with hot water, and dried (3·53 g.). The aqueous filtrate and washings, on cooling, deposited a further 0·052 g. of *p*-phenylphenol (total yield 3·58 g.; m. p. and mixed m. p. 167°). An aliquot part of the filtrate on titration with bromine indicated the presence of *ca.* 0·5 g. of phenol in all of the filtrate; actual extraction yielded 0·47 g. of phenol. Fission amounted therefore to 81 moles %.

p-tert.-*Butyldiphenyl Ether.*—Cleavage of this ether (18 g.) afforded phenolic materials which were taken up in aqueous potassium hydroxide and isolated in the usual manner, giving a liquid which readily crystallised (2·4 g.), m. p. 98—100°, alone or mixed with *p-tert.*-butylphenol.

Iodometric Titration (cf. Redman *et al.*, *loc. cit.*).—To 10 ml. of an approx. 0·03N-aqueous solution of the phenolic mixture were added 15 ml. of N-sodium hydrogen carbonate, followed by approx. 20% excess of 0·05N-iodine. The mixture was vigorously shaken for one minute, then acidified with 15 ml. of 2N-sulphuric acid, and the excess of iodine back-titrated with 0·1N-sodium thiosulphate. For mixtures of *o*- and *p*-chlorophenol and phenol, a 50—100% excess of iodine was necessary.

RESULTS AND DISCUSSION

The results of fission experiments (Table, column 5) present a contrast to those obtained by sodium in liquid ammonia (column 6; Sowa *et al.*, *loc. cit.*). This is not unexpected considering the differing nature of the reaction mechanisms. The latter involve attack of a nucleophilic reagent, and electron-attracting groups are expected to facilitate fission on the side of the substituted ring. Thus the order of activating influence is $p\text{-NH}_2 < p\text{-OMe} < p\text{-Me} < \text{H} < p\text{-CO}_2\text{Na}$, in accordance with the known electronic effects of these groups. A free radical, however, being electrically neutral, attacks an unperturbed molecule (Waters, *Trans. Faraday Soc.*, 1941, **37**, 772; *J.*, 1948, 727); the state of polarisation of the molecule is therefore no longer important in determining the course of the reaction, and resonance-stabilisation of the reaction intermediates becomes the controlling factor. This has recently been amply demonstrated in many homolytic reactions, *e.g.*, free-radical substitution reactions of aromatic substances, in which the nitro-group is mainly *ortho-para*-directing (Hey, Nechvatal, and Robinson, *J.*, 1951, 2892; DeTar and Scheifele, *J. Amer. Chem. Soc.*, 1951, **73**, 1442), mercuration of nitrobenzene under non-polar conditions, in which all three (*o*-, *m*-, and *p*-)positions are attacked (Klapproth and Westheimer, *ibid.*, 1950, **72**, 4461), and addition of aldehydes and polyhalogenomethanes to olefins in which high specificity in the direction of addition is exhibited (Patrick, *J. Org. Chem.*, 1952, **17**, 1009, 1269; Haszeldine and Steele, *J.*, 1953, 1199).

Fission of $R{\cdot}C_6H_4{\cdot}O{\cdot}C_6H_5$.

R	Total fission (mole %)	Yield of $R{\cdot}C_6H_4OH$ (mole %)			Fission by $Na–NH_3$ (mole %)
		Iodometric titration	Microanalysis	Mean	
o-Me	25	80	—	80	53
m-Me	36	~100	—	~100	62
p-Me	65	91	—	91	75
o-OMe	57	—	88	88	45
m-OMe	58	—	95	95	47
p-OMe	50	—	84	84 *	81
o-Cl	52	9	6	8	—
m-Cl	46	—	33	33	—
p-Cl	36, 34	—, 73	76, 73	76, 73	—
p-Bu^t	18	—	—	~100	—
p-Ph	43	—	—	81	—
p-NH_2	—	—	—	—	99
p-CO_2Na	—	—	—	—	0

* The cleavage product of this ether was described by Kharasch and Huang (*loc. cit.*) as " mostly phenol." This was based on the report (Hlasiwetz and Habermann, *Annalen*, 1875, **177**, 340), since discovered by one of us to be erroneous, that *p*-methoxyphenol was not volatile in steam. The phenolic mixture obtained was steam-distilled and the volatile fraction so obtained was titrated as phenol.

If, as postulated by Kharasch and Huang (*loc. cit.*), fission is brought about by the agency of free hydrogen atoms, two possible routes for the fission of diphenyl ether might be represented as follows :

$$C_6H_5{\cdot}O{\cdot}C_6H_5 + H{\cdot} \begin{array}{l} \nearrow C_6H_5{\cdot}O{\cdot} + C_6H_6 \quad \text{(i)} \\ \searrow C_6H_5{\cdot}OH + C_6H_5{\cdot} \quad \text{(ii)} \end{array}$$

These are not intended to depict the actual mechanism of the fission, but rather to indicate the intermediates that might be involved (see footnote, p. 674 of the preceding reference), and the isolation of benzene in addition to phenolic products in one cleavage experiment herein reported can be considered experimental evidence of the postulation of such intermediates. Of the two possible intermediates, the aryloxy- or the aryl radical, there is, apart from resonance considerations, ample experimental evidence to show that the former is comparatively much more stable. Thus, free aryls are extremely reactive (Hey and Waters, *Chem. Reviews*, 1937, **21**, 169), while aryloxy-radicals exhibit properties, *e.g.*, dimerisation (Cosgrove and Waters, *J.*, 1951, 388, 1726), consistent with a less reactive nature; in fact, certain long-lived radicals of this type have actually been prepared (*e.g.*, see Fieser and Young, *J. Amer. Chem. Soc.*, 1932, **54**, 4095). Moreover, it is well known that phenols are effective inhibitors for radical-chain reactions and the mechanism of inhibition has been shown (Waters and Wickham-Jones, *J.*, 1951, 812; 1952, 2421) to involve destruction of the chain-initiating radical $R'{\cdot}$ (*e.g.*, $C_6H_5{\cdot}$, $CH_3{\cdot}$) by a process of radical transfer with the formation of aryloxy-radicals ($R'{\cdot} + R{\cdot}C_6H_4{\cdot}OH \longrightarrow R{\cdot}C_6H_4{\cdot}O{\cdot}$) which must therefore be energetically more favourable. It follows that of the two possible routes of fission portrayed above, (i) is preferred. In a monosubstituted diphenyl ether $R{\cdot}C_6H_4{\cdot}O{\cdot}C_6H_5$, therefore, fission would take place depending on the relative stabilities of the aryloxy-radicals $R{\cdot}C_6H_4{\cdot}O{\cdot}$ and $C_6H_5{\cdot}O{\cdot}$, and substituents R which stabilise the radical $R{\cdot}C_6H_4{\cdot}O{\cdot}$ would increase the yield of $R{\cdot}C_6H_4{\cdot}OH$. Such a postulate appears to be in harmony with the results since, according to the generally accepted theory (Ingold, *Trans. Faraday Soc.*, 1934, **30**, 52), aryloxy-radicals are stabilised by electron-repelling substituents. Accordingly, *o*- and *p*-methyl as well as *o*- and *p*-methoxy-groups [all of which are electron-repelling, operating either by concerted inductive and mesomeric (hyperconjugative) effects (+*I*, +*M*), or by two opposing effects one of which predominates (+*M* > −*I*)] have all been found to lead to extensive formation of the cresols or methoxyphenols. The *m*-methyl and *p*-*tert.*-butyl group exemplify the effect of a purely inductive, and the *p*-phenyl a largely mesomeric, mechanism. The chloro-ethers perhaps yield results of greatest significance. Thus the cleavage product of the *meta*-isomer reflects the −*I* effect of the *m*-chlorine atom, while the *p*-chlorine is clearly to be designated (+*M* > −*I*). In the case of the *o*-chlorine atom, however, although its greater inductive effect, coupled with a diminished mesomeric one, as compared with the *p*-chlorine, satisfactorily explains the reversal of the direction of cleavage, the extent to which this takes place seems too great to be accommodated by these electronic effects alone and strongly suggests that a proximity factor, the exact nature of which is yet obscure, is also in operation. The *m*-methoxy-group appears to be anomalous and no explanation can at present be given.

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UNIVERSITY OF MALAYA, SINGAPORE, 10.

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