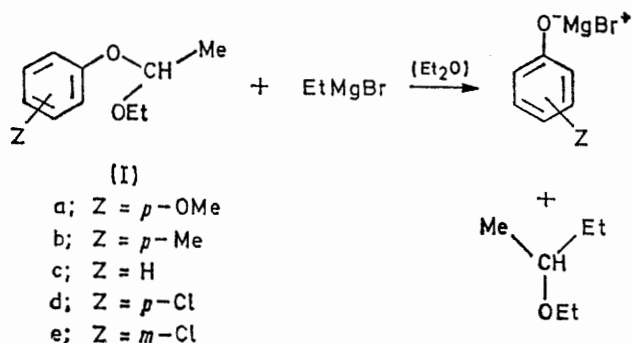


Cleavage of Carbon–Oxygen Single Bonds in the Reaction of Aryl Ethyl Acetals with Ethylmagnesium Bromide in Diethyl Ether. A Kinetic Study

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Acetaldehyde ethyl phenyl acetal and its *p*-methoxy-, *p*-methyl-, *p*-chloro-, and *m*-chloro-substituted derivatives were treated with ethylmagnesium bromide in diethyl ether. A substitution took place producing, after hydrolysis, phenols and ethyl *s*-butyl ether. Kinetic measurements were effected in the temperature range 0–40 °C. Second-order rate coefficients were correlated with Hammett σ values, giving $\rho + 2.35$ (30 °C). The nucleophilic character of the reaction is discussed.

GRIGNARD reagents are often unreactive towards C–O single bonds when they are complexed and dissolved by common ether solvents. However in some classes of compounds (acetals, orthoesters, epoxides) the C–O bond may be cleaved by Grignard reagents even in diethyl ether solution.¹ This is the case for the reaction of acetaldehyde aryl ethyl acetals (I) with ethylmagnesium



bromide, which was the object of this investigation. A partial report has been given.²

RESULTS AND DISCUSSION

Acetals (I), some of which have been previously described, were obtained as liquids. Some of their elemental analyses were affected by larger errors than usual, and a purity check by g.l.c. was not possible because of decomposition on the column with formation mainly of ethyl vinyl ether and of the phenol employed for the synthesis. However, the i.r. spectra showed no absorption in the OH region, the u.v. spectra were free of the phenols bands, and the n.m.r. spectra (Table I) corresponded to the structure of (I) without extra resonances. Substituted acetals remained unaltered for a few weeks; the unsubstituted compound (Ic) was even more stable.

The reaction of (I) with the Grignard reagent proceeded as indicated, *i.e.* as a displacement. Analogous reactions in homogeneous ether solution occur also in the case of

2-OR- and 2,2-(OR)₂-benzodioxols (R = Me, Et, or Ph).³ In principle, an elimination reaction could also take place, leading to phenol, ethyl vinyl ether, and ethane; moreover, since the Grignard reagent was in excess, it could react with the vinyl ether giving rise to *s*-butyl ethyl ether. To test this possibility, corresponding to substitution *via* elimination–addition, ethane was looked for in the products from (Ic) and from (Id): none was found. Also, it has been checked that ethyl vinyl ether does not react with ethylmagnesium bromide to give *s*-butyl ethyl ether, under the conditions of the displacement.

Kinetic measurements were performed in the range 0–40 °C, in most cases using diethyl ether solutions *ca.* 0.1M in acetal and 0.8–0.9M in the Grignard reagent.

TABLE I
 N.m.r.^a and u.v.^b spectral parameters of acetals

	Acetals				
	(Ia)	(Ib)	(Ic)	(Id)	(Ie)
Aromatic protons	6.54—	6.64—	6.65—	6.67—	6.62—
CH	6.84 (m)	6.85 (m)	7.14 (m)	7.06 (m)	6.94 (m)
CH ₂	5.02 (q)	5.07 (q)	5.14 (q)	5.11 (q)	5.11 (q)
(CH) ₂ CH ₃	3.28 (q)	3.42 (q)	3.44 (q)	3.42 (q)	3.38 (q)
(CH ₂)CH ₃	1.27 (d)	1.26 (d)	1.28 (d)	1.32 (d)	1.26 (d)
λ _{max} /nm	1.02 (t)	1.00 (t)	1.00 (t)	1.02 (t)	1.00 (t)
ε	286	278	269	284	272
	2 260	1 320	1 200	1 250	1 210

^a δ (Pure liquids) from hexamethyldisiloxane as internal standard. ^b In diethyl ether (only the most intense band of each compound is given).

The latter concentration is regarded as the formal concentration of EtMgBr, not accounting for the Schlenk and association equilibria. In diethyl ether solutions of the given concentration the Grignard reagent is actually a complex mixture, where the prevailing species appear to be polymeric (EtMgBr, OEt₂)_n entities.^{1d,4} The use of a narrow range of concentrations should assure the near-constancy of the composition of the mixture. Kinetic results obtained under these conditions were well interpreted by a second-order rate equation, first order in each reactant. Rate coefficients

¹ (a) M. S. Kharasch and O. Reinmuth, 'Grignard Reactions of Non-metallic Substances,' Prentice-Hall, New York, 1954, ch. 15; (b) E. G. Rochow, D. T. Hurd, and R. N. Lewis, 'The Chemistry of Organometallic Compounds,' Wiley, New York, 1957, p. 276; (c) 'The Chemistry of the Ether Linkage,' ed. S. Patai, Interscience, New York, 1967; (d) E. C. Ashby, *Organometallic Chem. Rev.*, 1970, **6B**, 73; (e) C. Blomberg, *ibid.*, 1971, **8B**, 341.

² P. Beltrame, G. Gelli, A. Lai, and A. Loi, *Communication No. 16*, Internat. Symposium on Nucleophilic Substitution, Pocono Manor, Pennsylvania, 1975.

³ S. Cabiddu, G. Gelli, and F. Sotgiu, *Ann. Chim. (Italy)*, 1971, **61**, 634.

⁴ M. B. Smith and W. E. Becker, *Tetrahedron*, 1966, **22**, 3 027.

are given in Table 2. Activation parameters are apparent values, which include the temperature dependence of the state of aggregation of the Grignard reagent.

TABLE 2

Rate coefficients ($10^5 k/1 \text{ mol}^{-1} \text{ s}^{-1}$)^a at various temperatures
([Acetal] ca. 0.1M; [Grignard reagent] 0.8–0.9M)

t/°C	Acetal				
	(Ia)	(Ib)	(Ic)	(Id)	(Ie)
0				0.224	0.568
10		0.107	0.219	1.047	2.37
20	0.300	0.424	1.043	4.32	8.58
25		0.585	0.753		
30	1.173	1.67	3.45	15.12	32.4
40		3.70	11.57		
log A	11.620	11.799	12.204	12.876	12.405
$\Delta E_a/kJ \text{ mol}^{-1}$	96.1	96.4	96.7	96.8	92.3

^a Standard deviations were, on the average, 3–4% of the k values.

A few kinetic runs were carried out using concentrations different from the standard values. Rate coefficients (see Experimental section) were particularly affected by variations in the acetal concentration, corresponding to a reaction order slightly larger than one with respect to this reagent. It is tentatively suggested that this is due to the change produced in the solvent when increasing amounts of acetal are added to diethyl ether.

The rate coefficients were dependent on temperature according to the Arrhenius equation. The five plots (Figure 1) had approximately the same slope, corresponding to an apparent activation energy $\Delta E_a = 94.5 \pm 2.5 \text{ kJ mol}^{-1}$. Use of the Eyring equation gives values of the activation entropy in the range from -31 to $-6 \text{ J K}^{-1} \text{ mol}^{-1}$.

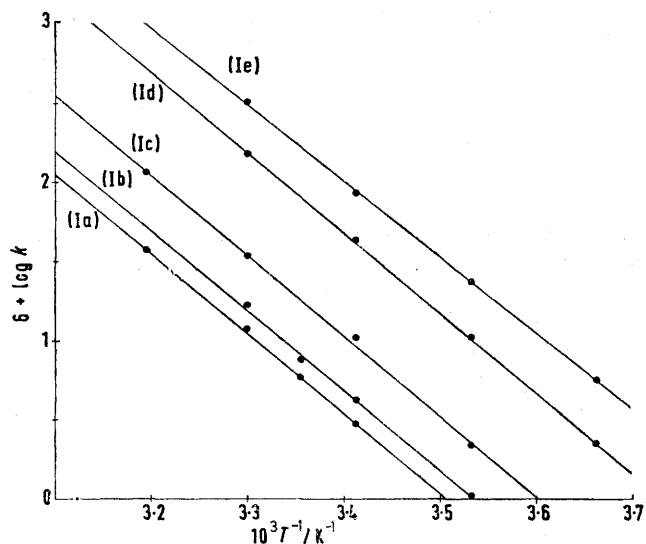


FIGURE 1 Arrhenius plots

When k values are correlated on a Hammett plot with standard values of σ_p and σ_m (Figure 2) the slope gives $\rho + 2.35 \pm 0.11$ (r 0.997) at 30°C .

Therefore, the predominant aspect of the reaction is nucleophilic attack of the Grignard reagent on the carbon atom of the acetal. The reaction might be

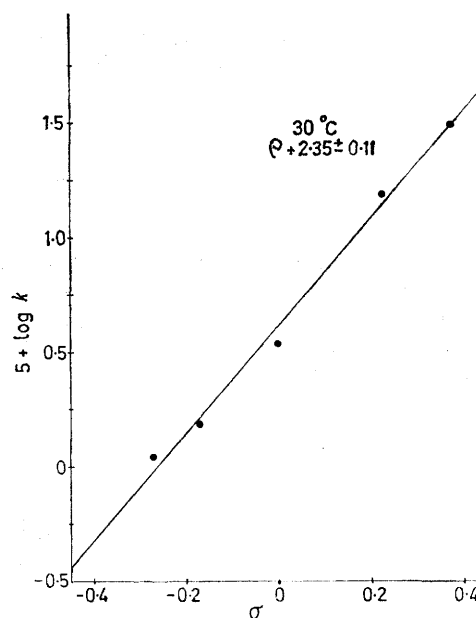
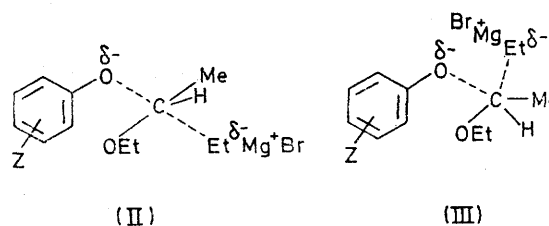


FIGURE 2 Hammett plot

considered as S_N2 -type; however it was not determined whether it occurs with inversion or retention of configuration at the asymmetric carbon of the acetal, the



enantiomers of compounds (I) being unavailable. Representing, as a first approximation, the Grignard reagent as EtMgBr , two alternative transition states may be indicated, of *anti*- (II) or *syn*- (III) conformation. The latter would differ from a four-centre transition state in having an advanced $\text{Et} \cdots \text{C}$ partial bond but only a weak interaction between Mg and O .

In any case, the positive ρ value corresponds to a stabilization of the incipient aryloxy anion which behaves as leaving group. For a comparison of substituent effects, available data⁵ about the quaternization of *NN*-dimethyl-*p*-anisidine with 4-substituted 2,6-dinitroanisoles in acetone at 35°C were correlated with σ values (σ^- for the nitro-substituent) obtaining $\rho + 2.28 \pm 0.19$. It should be considered that the leaving group in the latter case is an aryloxy anion stabilized by two *o*-nitro-groups, so that the extra stabilization by the *para*-substituents represents only a lower limit.

⁵ E. Hertel and H. Lüthmann, *Z. Elektrochem.*, 1939, **45**, 405.

Another possible comparison is with the ionization equilibrium of phenols. In water this has $\rho + 2.11$.⁶ In an aprotic solvent like diethyl ether the ρ constant should be higher; therefore the value 2.11 represents a lower limit of the substituent effect in ether.

In the light of these comparisons, the value ρ 2.35 found for the present reaction is not really large, although it is sufficient to define the nucleophilic character of the displacement. Much lower ρ values are reported for the attack of Grignard reagents on aryl ketones.⁷

EXPERIMENTAL

Materials.—Ethylmagnesium bromide was prepared in the standard way using Merck dried diethyl ether. The reagent was titrated by EDTA-complexometric and gas-volumetric methods. Substituted phenols were commercial products. Ethyl *s*-butyl ether was prepared according to the literature.⁸

U.v. spectra were taken either on a Perkin-Elmer 356 or a Pye-Unicam SP 700 instrument. N.m.r. spectra were recorded on a Varian HA-100 instrument. G.l.c. analyses were made on Carbowax 1500 5% columns at 50–180 °C with a C. Erba Fractovap GT chromatograph (flame ionization detector).

Acetals.—Acetaldehyde ethyl phenyl acetal (Ic) was prepared⁹ from phenol and ethyl vinyl ether. Substituted acetals were analogously obtained from the corresponding phenols. Yields were *ca.* 30%. Spectral data are given in Table 1. The ethyl 4-methoxyphenyl acetal (Ia) had b.p. 138–140 °C at 24 mmHg (lit.,¹⁰ 116–120° at 3 mmHg), n_D^{16} 1.5012 (Found: C, 68.0; H, 8.5. Calc. for $C_{11}H_{16}O_3$: C, 67.3; H, 8.2%). The ethyl 4-methylphenyl acetal (Ib) had b.p. 108–110 °C at 14 mmHg, n_D^{16} 1.4984 (Found: C, 73.1; H, 8.9. $C_{11}H_{16}O_2$ requires C, 73.3; H, 8.95%). The 4-chlorophenyl ethyl acetal (Id) had b.p. 120 °C at 3 mmHg, n_D^{16} 1.5125 (Found: C, 58.6; H, 6.9. $C_{10}H_{13}O_2Cl$ requires C, 59.85; H, 6.5%). The 3-chlorophenyl ethyl acetal (Ie) had b.p. 115 °C at 3 mmHg, n_D^{16} 1.5102 (Found: C, 60.4; H, 7.3%).

Products.—Reactions were usually carried out and products separated under the conditions of the kinetic runs. Yields of phenolic derivatives, measured both by g.l.c. and u.v. analyses, were quantitative. Ethyl *s*-butyl ether yields were evaluated by g.l.c. and found to be from 70 to 90%.

⁶ J. E. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions,' Wiley, New York, 1963, p. 178.

⁷ R. N. Lewis and J. R. Wright, *J. Amer. Chem. Soc.*, 1952, **74**, 1257; M. Anteuins and J. van Schoote, *Bull. Soc. chim. belges*, 1963, **72**, 776; P. Geneste, G. Lamaty, and J. P. Roque, *Tetrahedron Letters*, 1970, 5007.

with respect to the acetal reacted. Reactions on compounds (Ic and d) were also carried out in *ca.* 0.5M solutions in a flask connected to a gas burette: no gas was collected during the reaction of the acetals.

After reaction of ethyl vinyl ether (0.1 mol) with ethylmagnesium bromide (0.1 mol) at room temperature during 3 days only ethyl vinyl ether, traces of unknown products, but no ethyl *s*-butyl ether were revealed by g.l.c.

Kinetics.—Substrates were weighed and known volumes of titrated Grignard reagent were added under nitrogen in Pyrex tubes with screw cap, in order to obtain 20 ml of solution in each tube. The tubes resisted slight excess of pressure. Thermostatting (± 0.1 °C) was achieved in a negligible time by comparison with the length of the reaction (2–360 h). Quenching of the reaction mixture was effected by ice-water containing buffered EDTA (pH 10). The phenolic fraction was removed by extraction with 5% NaOH and each acetal was determined in the residue, after appropriate dilution, by u.v. analysis at the wavelength of the most intense absorption. It was verified that the Lambert-Beer equation was followed in the range 10^{-4} – 10^{-3} M with correlation coefficients $r \geq 0.999$. Rate coefficients

TABLE 3
Rate coefficients in different conditions

Z	<i>t</i> /°C	Initial concentrations		$10^6 k / 1 \text{ mol}^{-1} \text{ s}^{-1}$	
		[Acetal]/M	[Grignard reagent]/M		
<i>p</i> -Me	30	0.28	0.87	2.27	
	H	10	0.30	0.89	0.301
		20	0.30	0.92	1.39
		30	0.30	0.87	5.40
	30	0.40	0.92	5.91	
H	30	0.10	0.40	3.87	
	<i>m</i> -Cl	30	0.10	0.54	28.6

were calculated by least-squares fitting to the second-order rate equation ($r > 0.995$). Reactions were carried out from 15 to 75% conversion.

Runs at reactant concentrations outside the standard range gave the results shown in Table 3.

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⁸ E. M. Marks, D. Lipkin, and B. Bettman, *J. Amer. Chem. Soc.*, 1937, **59**, 946.

⁹ M. F. Shotakovskii, *Zhur. obshchei Khim.*, 1950, **20**, 608 (*Chem. Abs.*, 1950, **44**, 7754).

¹⁰ R. Alquier, *Bull. Soc. chim. France*, 1943, **10**, 197.