Aryl and Heteroaryl Substituent Effects in Reductions and Solvolysis Reactions

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Rates of reduction by sodium borohydride of a series of substituted acetophenones and of acetyl-furans, -pyrroles, and -thiophens have been measured. The results fit the Yukawa–Tsuno equation with ρ 2·68, r 0·28. For the heterocyclic systems σ^+ values are derived from rate constants for solvolysis of the corresponding carbinyl chlorides and σ values from rate constants for hydrolysis of the carboxylic esters.

THE range of reactivities encountered with simple aromatic compounds is large and presents some difficulties in making direct quantitative comparisons. Thus the rate constants for solvolysis[1] of phenyl and *p*-dimethylaminophenyl acetate in 30% aqueous ethanol differ by a factor of 10^{10}. In an attempt to develop a reaction system applicable directly to a wide range of benzenoid derivatives and which might also be conveniently extended to the reactive five-membered heteroaromatic compounds, the reduction of acetyl derivatives by sodium borohydride has been examined. This reaction has been shown by Brown *et al.*[2-4] to respond to structural changes in the carbonyl compound in a manner related to the effects of similar changes on the solvolysis of the corresponding aralkyl chlorides. For comparison purposes the solvolyses of a number of 1-arylethyl chlorides were also examined.

TABLE 1

Kinetic parameters for sodium borohydride reduction of aryl methyl ketones in propan-2-ol at 30°

Ketone	10^4k/ l mol^{-1} s^{-1}	Relative rate	$\Delta H^‡$/ kcal mol^{-1}	$\Delta S^‡$/ cal mol^{-1} K^{-1}
Acetophenone	20·1 [a]	1·00	11·7	−32·5
p-Bromoacetophenone	87·1 [a]	4·35	9·1	−38·1
m-Methylacetophenone	14·1 [a]	0·71	10·9	−35·6
p-Methylacetophenone	8·13 [a]	0·41	12·9	−30·0
p-Methoxyacetophenone	1·93 [a]	0·096	11·5	−37·4
p-Dimethylaminoacetophenone	0·17 [b]	0·009	19·8	−15·2
p-Aminoacetophenone	0·09 [b]	0·005	18·6	−20·1
2-Acetylfuran	27·1 [a]	1·36	11·7	−31·6
3-Acetylfuran	6·36 [a]	0·32	13·4	−28·8
2-Acetylthiophen	6·15 [a]	0·31	14·7	−24·7
3-Acetylthiophen	8·94 [a]	0·44	12·9	−29·7
2-Acetylpyrrole	0·10 [b]	0·005	12·3	−41·0
3-Acetylpyrrole	0·04 [b]	0·002	12·6	−41·6
N-Methyl-2-acetylpyrrole	0·11 [b]	0·006	13·8	−35·9
N-Methyl-3-acetylpyrrole	0·02 [b]	0·001	10·6	−49·9

[a] Standard error of estimate, ±1·5%. [b] Standard error of estimate, ±5%.

TABLE 2

Kinetic parameters for the solvolysis of 1-arylethyl chlorides in 95% acetone at 45°

Aryl group	10^5k/s^{-1}	Relative rate	$\Delta H^‡$/kcal mol^{-1}	$\Delta S^‡$/cal mol^{-1} K^{-1}
Phenyl	0·0084 [a]	1·0	22·2	−12·7
p-Tolyl	0·335 [a]	39·8	19·6	−22·2
p-Anisyl	282 [a]	33,600	15·0	−23·1
2-Furyl	389 [a]	46,300	15·8	−20·2
3-Furyl	2·67 [a]	316	15·1	−31·8
2-Thienyl	135 [a]	16,100	13·9	−28·0
3-Thienyl	2·62 [a]	312	17·4	−24·8
p-Bromophenyl	0·00020	0·24		
p-Chlorophenyl	0·0026	0·31		
m-Tolyl	0·016	1·90		
m-Chlorophenyl	0·00011	0·013		
m-Bromophenyl	0·00008	0·01		

[a] Standard error of estimate, ±1·5%.

RESULTS

(a) *Borohydride Reduction.*—The results (Table 1) were not affected by the side reactions encountered with highly reactive carbonyl compounds[5] and are in satisfactory agreement with the values reported previously for acetophenone and its *p*-bromo, *m*-, and *p*-methyl derivatives.[6] The result for *p*-methoxyacetophenone differs from that obtained by the use of the spectroscopic method:[6] for

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slow reactions this method appears liable to random variation, possibly arising from autoxidation of the solvent, and in our hands gave results of poor reproducibility.

(b) *Solvolyses*.—The reactions showed good first order kinetics and the results (Table 2) are in agreement with those reported by Yukawa *et al.*[7] for 80% aqueous acetone. The greater reactivity of the heterocyclic carbinyl chlorides gave convenient rates of solvolysis only in 95% aqueous acetone. For purposes of comparison, rate constants for 95% aqueous acetone for the bromo- and chloro-phenyl compounds were calculated from the literature values [7] for 80% acetone by using the relative rate factors shown by the tolyl and *p*-methoxyphenyl derivatives.

DISCUSSION

The solvolysis of 1-phenylethyl chloride in aqueous organic solvents is known to proceed through a limiting S_N1 mechanism.[8,9] A similar mechanism has been demonstrated for a wide range of substituted phenylethyl chlorides.[10] The effects of substituents in the solvolysis of the related t-cumyl chlorides provide the basis for the σ^+ series of substituent constants.[11] Plots of log k_{solv} against σ^+ are linear both for phenylethyl acetates [1] and for restricted ranges of phenylethyl chlorides.[12] The present results for substituted phenylethyl chloride (Table 2) extend the available data to more electron-releasing substituents and so provide a better test of the validity of the relationship; good correlation (correlation coefficient 0·992; standard deviation 0·21) with ρ −5·37 is observed.* In common with related solvolyses, the variations in $\Delta H^\ddagger$ and $\Delta S^\ddagger$ show no proportionality.[1,14]

By interpolation of the results for the solvolyses of the heterocyclic derivatives, estimates of the σ^+ constants for the heterocyclic rings were obtained. The results (Table 3) are in good agreement with those obtained from other solvolytic,[1,15] pyrolytic,[16] and substitution [17] reactions.

The reaction of sodium borohydride with ketones in propan-2-ol proceeds either by direct nucleophilic attack or by pre-equilibrium complex formation followed by rate determining hydride transfer.[2-4,18] The importance of steric factors and of substituent polar effects in the reduction of alkyl and aralkyl ketones is well established.[2-6,18-20] With aromatic ketones possessing similar steric environments for the carbonyl group, the reactivity is largely dependent on polar factors. Thus rate constants for reduction of fluorenones and acetophenones are reported [6,21] to be well correlated by the Hammett equation. The present results (Table 1) extend the range of acetophenones carrying electron-releasing substituents and for these compounds the Hammett plot is curved. A linear plot for the complete series of acetophenones, including the values reported by Bowden and Hardy [6] and the heterocyclic ketones is obtained by using the Yukawa–Tsuno equation,[13] log $k/k_0 = \rho(1 - r)\sigma + r\sigma^+$ with ρ 2·68, r 0·28 (correlation coefficient 0·98; standard deviation 0·12; multiple regression analysis indicates that both terms are significant at better than the 0·5% level).

TABLE 3

Substituent constants for heterocyclic systems

	σ	σ^+
2-Furyl	0·32 ± 0·08	−0·85 ± 0·08
3-Furyl	0·04 ± 0·08	−0·44 ± 0·08
2-Thienyl	0·03 ± 0·08	−0·76 ± 0·08
3-Thienyl	0·04 ± 0·08	−0·44 ± 0·08
2-Pyrrolyl	−0·58 ± 0·08	−1·61 ± 0·30 [a]
3-Pyrrolyl	−0·94 ± 0·08	−1·20 ± 0·30 [a]

[a] Calculated from the rate constant for reduction.

Values of σ constants for the heterocyclic groups (Table 3) were needed for this plot. They were obtained from the rate constants for alkaline hydrolysis of the carboxylic esters in aqueous acetone [22] by comparison with those for substituted ethyl benzoates [23] (ρ 2·33); results for hydrolyses in aqueous dioxan [24] and in aqueous ethanol [25] give similar values. The satisfactory fit of the rate constants for borohydride reduction using these values supports the validity of this

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* Use of the Yukawa–Tsuno equation [7,13] for this correlation shows a small increase in correlation (0·994) with ρ −4·83, r 1·28, but multiple regression analysis indicates that the improvement is only valid at the 15% level.

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procedure; no satisfactory correlation can be based on the pK_a values for the heterocyclic carboxylic acids [22,24-26] for which unusual enthalpy and entropy changes accompany dissociation.[27]

By using σ constants derived from hydrolysis of pyrrole-2- and -3-carboxylic esters,[22] estimates of the corresponding σ^+ constants were obtained from the rate constants for borohydride reduction (Table **3**). Particularly noteworthy is the spread of values of σ and σ^+ for all the heterocyclic systems and the correspondingly large negative values of $\Delta\sigma^+$.

An attempt to relate structural effects for the solvolysis and reduction reactions by plotting log k_{solv} against log k_{redn} showed poor linearity. Although similar plots for alkyl and aralkyl systems have given fair straight lines,[4,20] considerable scatter has been reported for bicyclic systems [19] in which the different steric requirements of the two reactions become evident. For aryl derivatives it is probable that the differing polar demands of the two reactions are the more important. It is readily shown that for reactions conforming to the Yukawa–Tsuno equation the displacement of points from linearity is proportional to $\Delta r \Delta\sigma^+$; the results in Tables **1** and **2** satisfy this relationship.

EXPERIMENTAL

Propan-2-ol was dried over calcium hydride and distilled from sodium borohydride. Redistilled acetone was dried over molecular sieves (Union Carbide, type 4A).

Ketones.—Commercially available ketones were recrystallised or redistilled before use and had physical properties agreeing well with literature values.

3-Acetylfuran,[28] b.p. 75—76° at 15 mmHg, m.p. 50—51°, 3-acetylthiophen,[29] m.p. 59—60°, and 3-acetylpyrrole,[30] m.p. 113°, were obtained by established methods. Alkylation of acetylpyrrole with methyl iodide (1 equiv.) in boiling acetone containing anhydrous potassium carbonate gave 2-acetyl-1-methylpyrrole, b.p. 64—66° at 3 mmHg, and 3-acetyl-1-methylpyrrole, b.p. 110° at 6 mmHg.

1-*Phenylethyl Chlorides.*—(a) *Alcohols.* Acetophenone (0·1 mol) in dry ether (150 ml) was added slowly to lithium aluminium hydride (0·11 equiv.) in ether (200 ml). After the reaction was complete the excess of hydride was decomposed by addition of ice, the resultant suspension was made alkaline and the product was extracted into ether giving the alcohol (82%), b.p. 42° at 0·2 mmHg, n_D^{25} 1·5245. Substituted phenyl alcohols were prepared similarly. 1-(3-Furyl)-, b.p. 33° at 0·03 mmHg, 1-(2-thienyl)-, b.p. 60° at 0·1 mmHg, 1-(2-pyrrolyl)-, b.p. 90° at 2·5 mmHg, and 1-[2-(1-methylpyrrolyl)]ethyl alcohol, b.p. 74° at 2 mmHg, were prepared by using reverse addition. 1-(2-Furyl)ethyl alcohol, b.p. 72° at 10 mmHg, was prepared [31] from furfural and 1-(3-thienyl)ethyl alcohol from 3-thienyllithium.[32] G.l.c. examination of the products of borohydride reduction of the ketones showed the only detectable product to be alcohol.

(b) 1-*Phenylethyl chlorides.*[14] 1-Phenylethyl alcohol was saturated with dry hydrogen chloride. The aqueous layer was removed and the residue was dried over calcium chloride and distilled giving the chloride, b.p. 70—73° at 10 mmHg. For solvolysis experiments the dried product was used without purification; substituted phenyl derivatives were prepared similarly. 1-Heteroarylethyl chlorides were prepared at −40° by the action of thionyl chloride on an ethereal solution of the alcohol.[33] The solvent was evaporated *in vacuo* at −15° and replaced by dry acetone: this process was repeated three times and the final solution was filtered through a short column of neutral alumina.

With 1-(2- and -(3-pyrrolyl)ethyl alcohols and 1-[2-(1-methylpyrrolyl)]ethyl alcohol even when the reaction was performed at −70° the solution immediately darkened in colour and no chloride could be detected.

Rate Measurements.—(a) *Reductions.* A solution of sodium borohydride in propan-2-ol (10 ml; 0·008—0·3M) was mixed with a solution of the ketone in propan-2-ol (10 ml; 0·05—0·18M) at the reaction temperature. At appropriate times, aliquot portions (2 ml) were withdrawn and titrated against potassium iodate.[18] Reactions were followed up to 85% completion; reproducible results giving good second-order plots ($r > 0·996$) were obtained for reactions run in triplicate and at least at three different temperatures in the range 0—72°.

(b) *Solvolyses.* 1-Arylethyl chloride in acetone (1 ml) was dissolved in acetone (94 ml) and the solution diluted with water (5 ml) at the reaction temperature. At appropriate times aliquot portions (5 ml) were placed in acetone (100 ml) and titrated against standard sodium hydroxide solution. Reactions were followed to 70% completion; reproducible results giving good first-order plots ($r > 0·995$) were obtained for reactions run in triplicate and at least at three different temperatures. Extraction of the product from a large scale solvolysis of 1-phenylethyl chloride gave material which by g.l.c. comparison was largely the corresponding carbinol.

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