Transmission of Substituent Effects through Unsaturated Systems. Part 6.[1] Kinetics of Reduction of β-Substituted α,β-Unsaturated Ketones with Sodium Borohydride

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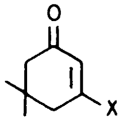
The rate constants for addition of sodium borohydride to 3-substituted 5,5-dimethylcyclohex-2-enones (**1**), *para*-substituted 3-phenylcyclohexenones (**2**), and *para*-substituted acetophenones (**3**) have been determined in an alkaline solution (NaOH, 0.025 mol l^{-1}) of water–dioxane (1 :1 v/v) at 298 K. The conjugated cyclohexenone systems (**1**) and (**2**) undergo exclusive 1,2-reduction in these conditions to produce the corresponding allylic alcohols. The regioselectivity of reduction is discussed. The linear free energy relationships obtained between the rate constants and σ_p or σ_p^+ confirm that these 3-substituted cyclohexenone structures are good models for the investigation of the substituent effects on the reactivity of ethylenic systems. Comparison of reaction constants for the three series leads to the conclusion that, as for borohydride reductions of acetophenone, the cyclohexenone reduction must have a late transition state in the final quarter of the reaction co-ordinate.

We have recently demonstrated that 5,5-dimethylcyclohex-2-enone (**1**) is an appropriate model to investigate the transmission of electronic substituent effects through a directly substituted ethylenic bond and we have established the applicability of Hammett-type relationships to describe several physical parameters of ground-state molecules[2-4] and acid–base equilibrium involving the carbonyl function.[1] The last step, presented here, is to look for the applicability of Hammett-style equations to an irreversible reaction linked to the carbonyl function. We have chosen reduction by borohydride. Indeed, this reaction of the carbonyl function is important synthetically[5-10] and, to our knowledge, in spite of extensive applications for conjugated carbonyl series, there was not at present a study of the quantitative influence of substituents on the rate of reduction of α,β-unsaturated ketones with substituents directly linked to the ethylene bond.[11-13] We have therefore measured the rate constants for the sodium borohydride reduction of series (**1**) and (**2**) and attempted to apply Hammett-type correlation analysis. In order to compare the transmission factors of ethylenic and phenyl groups, we have extended this study to *para*-substituted acetophenones (**3**).

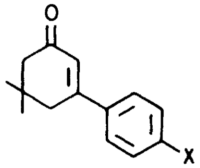
Experimental

Substrates.—The preparation of cyclohexenones (**1**) and (**2**) and their spectroscopic properties are described in refs. 3 and 14. All the acetophenones were commercially available.

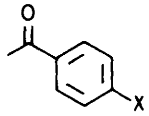
Kinetic Measurements.—The rate of reduction of enones (**1**) and (**2**) and acetophenones (**3**) by sodium borohydride in alkaline water–dioxane (1 :1 v/v; 0.025M-NaOH) at 298 K was monitored spectrophotometrically by observing the reduction in absorbance with time, at the u.v. wavelength of maximum absorption of the substrate. This general procedure was previously reported for the reduction of saturated ketones.[15] In order to simplify the kinetics and to obtain only the 1,2-reduction of the conjugated ketones, a large excess of borohydride (*ca.* 0.3 mol l^{-1}) over substrate (*ca.* 10^{-5} mol l^{-1}) must always be employed. Thus, the pseudo-first-order constants were converted into second-order rate constants by division by the borohydride concentration. Most reactions were run at least in duplicate, the reproductibility being ± 3%.



(**1**)



(**2**)



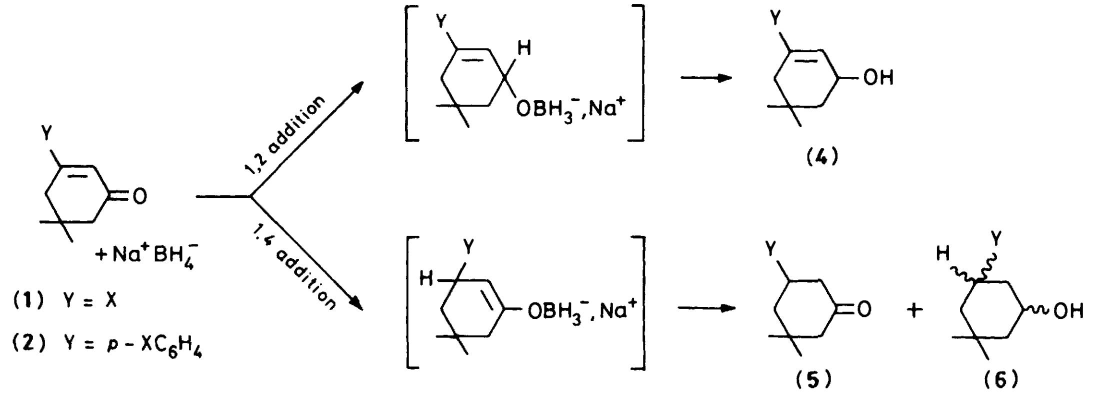
(**3**)

Characterisation of Reaction Products.—The 1,4- and 1,2-reduction products of enones (**1**) and (**2**) were identified by comparison of g.l.c. retention times. In order to obtain the experimental conditions for the exclusive 1,2-reduction, three concentrations, 0.1, 0.5, and 5M-borohydride in alkaline water–dioxane were used with an enone concentration closed to 10^{-3}M. G.l.c. analyses were performed on a Carlo Erba Fractovap 2400 V apparatus using Carbowax 20 M (10%, 1% KOH) and OV 17 (10%) glass columns (2 m, 4 mm), respectively, for series (**1**) and (**2**).

Results and Discussion

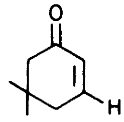
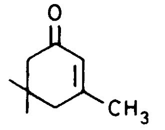
Regioselectivity of Reductions.—It is well known that the expected products of borohydride reduction of α-enones are allylic alcohols (**4**) derived from C-1 attack (1,2-reduction) and saturated ketones (**5**) and alcohols (**6**) from C-3 attack (1,4-reduction).[6,7,11,12,16-20] The presence of these two competitive additions is undoubtedly the reason for the difficulty in studying substituent effects on the rate of reduction of α-enones.[12,13]

The stereoselectivity is strongly dependent on the nature and concentration of borohydride, the effects of salt concentration, and the nature of the salt, solvents, and structure of substrates.[7,16-20] Using those different parameters, it is therefore possible to favour one attack over the other and even to obtain



Scheme.

Table 1. Borohydride concentration effect on the stereoselectivity of reduction ([ketone] $\simeq 10^{-3}$ mol l^{-1})

Ketone	[NaBH$_4$]/mol l^{-1}	log [NaBH$_4$]/[ketone]	C-1 attack (%)	C-3 attack (%)
	0.1	2.0	22	78
	0.5	2.7	34	66
	5	3.7	56	44
	0.1	2.0	46	54
	0.5	2.7	85	15
	5	3.7	100	0

regioselectivity. Thus, with sodium borohydride, it is known that when the borohydride concentration and the ratio [Na$^+$]/[ketone] are increased, 1,2-addition is favoured[17] and the interference of alkoxyborohydrides leading to 1,4-addition is avoided.[8,19–23] Besides, a high concentration of alkaline Na$^+$ cation gives a salt effect which increases 1,2 addition.[17] Finally, the catalytic effect of protic solvent can favour the reduction of the carbonyl group.[7,19,24] Concerning the substrate, it has been demonstrated that the ratio of 1,2- to 1,4-addition increases when a substituent is at the 3 position in cyclohexenone.[16,20] Thus, in alkaline water–dioxane with ketone and reactant concentration of 10^{-3} and 0.5 mol l^{-1} respectively, chromatographic analysis shows only 1,2-addition for all the ketones (**1**) and (**2**) except for isophorone (X = CH$_3$) and the unsubstituted compound in series (**1**) which gives 85 and 34% allylic alcohol, respectively, the remainder being the saturated alcohol.* The results observed for these two ketones at three NaBH$_4$ concentrations are reported in Table 1.

Moreover, the variation of these values indicates that with the concentrations used for this kinetic study, these two compounds can undergo exclusively 1,2-reduction leading to the allylic alcohols. Thus, under the kinetic conditions, all ketones (**1**) and (**2**) undergo a regiospecific reduction of the carbonyl function.

Since with substrate and reactant concentrations of 10^{-3} and 0.5 mol l^{-1}, respectively, only two compounds in series (**1**) with substituents X = H and CH$_3$ permit the observation of both 1,2- and 1,4-additions, we conclude that, opposite to the results for 3-methylene-[11] and 3-benzylidene-camphors,[12] there is no relationship between the proportions of 1,2- and 1,4-addition and the electronic effect of substituents on the double bond. The lack of a steric effect at C-3 seems to favour 1,4-addition, in agreement with observations for the reduction of β-substituted and β-unsubstituted α-enones.[13,16,20]

Hammett-type Relationships.—The Hammett-type relationships were applied to the rate coefficients listed in Table 2. The σ_p and σ_p^+ values recommended by McDaniel and Brown,[25] and Brown and Okamoto,[26] respectively, were used and the results of the correlations are shown in Tables 3 and 4. For series (**2**) and (**3**), the best correlations were obtained using the σ scale in agreement with the result of Cockerill and Rackham for 1,5-diarylpenta-1,4-dien-3-ones[13] and Bowden and Hardy for acetophenones.[28] On the other hand, the σ^+ scale must be used with the cyclohexenones directly substituted on the double bond. This discrepancy is easily understood, on the one hand, if we consider the definitions of the σ and σ^+ scale[29] and, on the other, if we assume that the transition state of the reduction is near the product[8] in the three series. Indeed, the use of σ^+ values means there is a large difference in the direct conjugation between the substituent and the function when we go between the initial state and the final state in an equilibrium or between the initial state and the transition state for an irreversible reaction, when this difference is weak using the classical σ scale. Now, in series (**1**), if there is a certain degree of direct conjugation between electron-releasing substituents and the electron-attracting carbonyl function solvated by a hydrogen bond in the initial state, this direct conjugation does not exist in the later transition state. On the other hand, with cyclohexenones (**2**)[2] as with acetophenones,[30] the torsion angle between the plane of the benzene system and that of an α-enone or acetyl system strongly decreases the mesomeric effect in the initial state and does not entail the use of the Brown–Okamoto scale.[26]

Also, the ρ coefficient of the reaction of acetophenones (2.62) is significantly lower than that given by Bowden and Hardy

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* The saturated ketones (**5**) have not been seen. This is explained by the fact that under the same experimental conditions, 3,3-dimethylcyclohexanone and 3,3,5-trimethylcyclohexanone have reduction rates around six-fold higher.

Table 2. Second-order rate constants for the reduction of series (**1**)—(**3**) with sodium borohydride in water–dioxane (50:50 v/v) and NaOH (0.025M) at 298 K

			Series (**1**)		Series (**2**)		Series (**3**)	
Substituent	σ_p	σ_p^+	$10^4\,k_2$/ l mol^{-1} s^{-1}	$-\log k_2$	$10^4\,k_2$/ l mol^{-1} s^{-1}	$-\log k_2$	$10^4\,k_2$/ l mol^{-1} s^{-1}	$-\log k_2$
H	0	0	47.9	2.320	17.5	2.757	34.27	2.465
NO_2	0.778	0.778			119	1.924	3 010	0.522
CN	0.66	0.659	6 170	0.210	90.4	2.044	6 660[b]	0.177[b]
F	0.062	−0.073			20.2	2.695	49.16	2.308
Cl	0.227	0.114	170	1.770	30.7	2.515	122	1.914
Br	0.232	0.150	89	2.048	30.3	2.519	158	1.802
C_6H_5	−0.01	−0.179	17.5	2.757	19.0	2.721		
CH_3	−0.17	−0.311	5.42	3.266	13.0	2.886	14.06	2.852
SC_2H_5	0.03	−0.604[c]	1.87	3.727				
OCH_3	−0.27	−0.778	0.290	4.538	9.1	3.041	4.35	3.362
OC_2H_5	−0.24	−0.82	0.215	4.668				
NH_2	−0.66	−1.30	*a*		3.3	3.481		

[a] The enaminoketone cannot be reduced under these conditions.[27] [b] We observe the reduction of the cyano group.[c] Value for SCH_3.

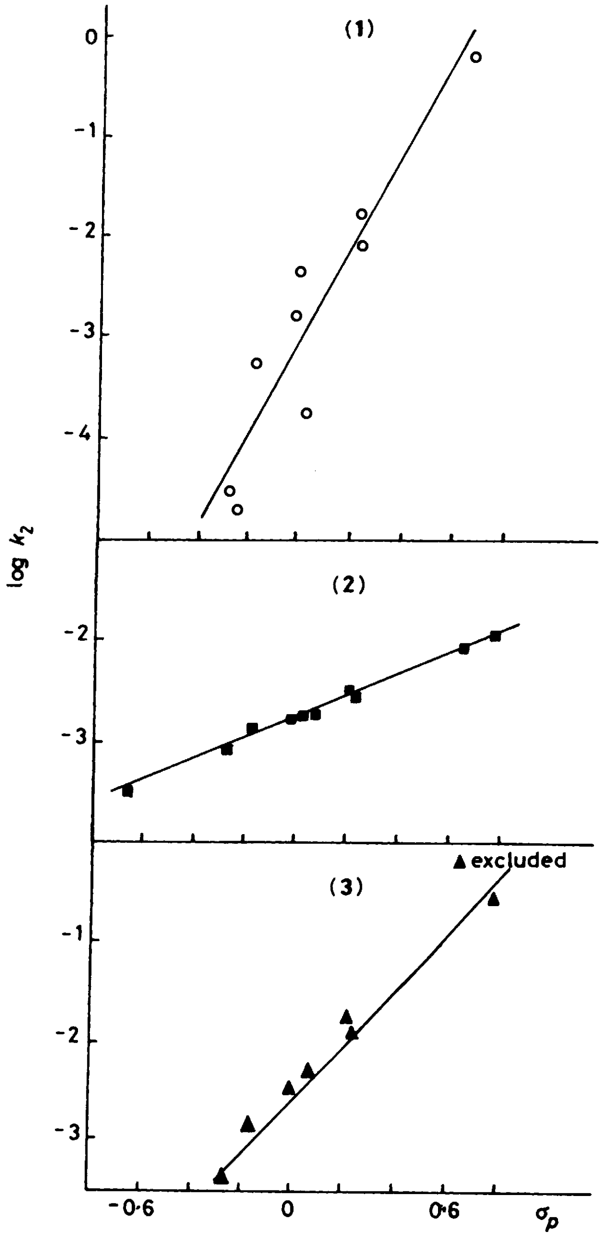

Figure 1. Plots of log k_2 *versus* σ_p for series (**1**)—(**3**)

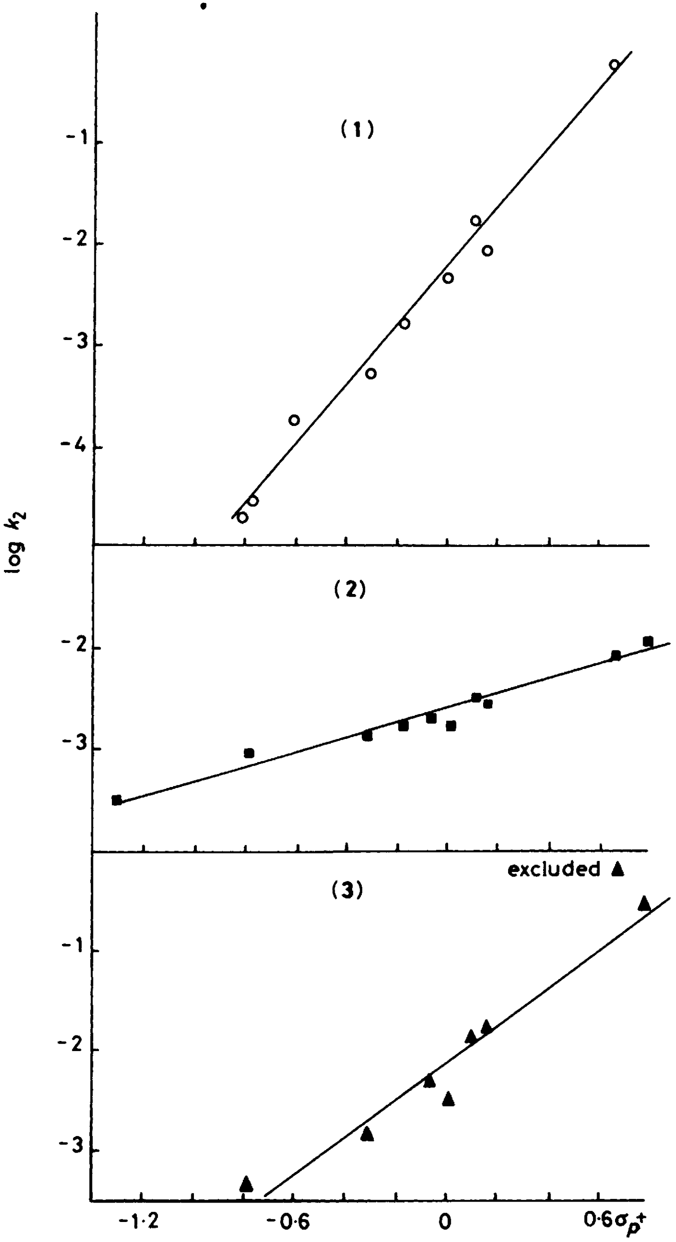

Figure 2. Plots of log k_2 *versus* σ_p^+ for series (**1**)—(**3**)

Table 3. Results of Hammett correlations $\log k_2 = \rho\sigma_p + h$

Equation	Series	ρ	h	n^a	r^b	s^c
(1)	(**1**)	4.560	−3.044	9	0.9343	0.542
(2)	(**2**)	1.068	−2.749	10	0.9987	0.025
(3)	(**3**)	2.615	−2.496	7^d	0.9953	0.096

[a] Number of points. [b] Correlation coefficient. [c] Standard deviation. [d] Cyano compound is excluded. The reduction occurs in part on the CN group.

Table 4. Results of Brown–Okamoto correlations $\log k_2 = \rho^+\sigma_p^+ + h$

Equation	Series	ρ^+	h	n^a	r^a	s^a
(4)	(**1**)	2.904	−2.241	9	0.9941	0.164
(5)	(**2**)	0.722	−2.591	10	0.9816	0.092
(6)	(**3**)	1.869	−2.143	7^a	0.9786	0.204

[a] See Table 3.

(3.06).[28] That agrees with which is expected for the solvent effect on the ρ coefficient for a change from water–dioxane to propan-2-ol.[29]

Comparison of the ρ and ρ^+ constants for series (**1**) and (**2**) leads to the transmission factor π_{ph} of the *p*-phenylene group. We obtain 0.23 and 0.25, respectively, from equations (1) and (2), and (4) and (5). These values are in good agreement with those obtained previously.[1] Moreover, comparison of the reaction constants in equations (2) and (3) shows that the transmission of the substituent effect is reduced by *ca.* 60% (π_{vinyl} 0.41) by insertion of the olefinic bond between the reaction site and substituent. The difference between the reaction constant for the ionisation of substituted benzoic acids (ρ 1.00) with that for *trans*-cinnamic acids (ρ 0.418)[31] in the same solvent again indicates a similar order of reduction in transmission by the olefinic double bond. The agreement of the π_{ph} and π_{vinyl} values obtained here with literature data suggests that, since the sodium borohydride reduction of acetophenones must have a late transition state in the final quarter of the reaction co-ordinate,[8] this may also be the case for 1,2-reduction of the carbonyl group in conjugated ketones (**1**) and (**2**).

Acknowledgements

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