The Validity of the Spectrophotometric Method for Determination of the Kinetics of the Reduction of Ketones with Sodium Borohydride

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The kinetics of reduction of a number of ketones by sodium borohydride have been followed spectroscopically and give good second-order plots with correlation coefficients *ca.* 0·999 and essentially zero intercepts at zero time. These plots yield satisfactorily reproducible rate constants over a range of concentrations. The results suggest that the spectral method is satisfactory for measurement of these kinetics. The values of the rate constants are in agreement with those previously obtained by potentiometric and chromatographic methods but considerably higher than those obtained by the iodate titration method.

In connection with our studies on the stereoselectivity of the reduction of cyclohexanones by sodium borohydride, it has been necessary to measure the kinetics of these reductions.[1,2] We have developed a convenient spectroscopic method [2] by following the disappearance of the n,π^* ketone band at *ca.* 285 nm. Since the publication of some of these results,[1] Rickborn and Wuesthoff [3] have reviewed the available kinetic methods for reduction of ketones with borohydride, and pointed out the discrepancy between results obtained by the original iodate titration method [4–7] and those obtained by potentiometric and chromatographic methods. They conclude that the titration method is not adequate. Since the very convenient spectral method was not included, we felt that it would be advantageous to compare results so obtained with those from other methods, both to investigate the validity of the spectral method, and to clarify further the discrepancy.

RESULTS AND DISCUSSION

The rate-controlling step in the reduction of ketones by sodium borohydride is transfer of the first hydride ion from boron to carbon,[5,8] and the second-order rate constant is considered to represent, within a few per cent., the value for this initial hydride transfer.[3] Rickborn and Wuesthoff [3] have shown that the potentiometric ($AgED^+$) and chromatographic (g.l.c.) methods give values of rate constants in good agreement with each other but considerably higher (as much as 50%) than those reported from the iodate titration method. We have subjected the spectral kinetic method to four criteria: (i) the reproducibility of rate constants under given conditions; (ii) the constancy of rate constants over a range of concentration; (iii) the correlation coefficients for individual runs; and (iv) the presence and magnitude of any non-zero intercepts (corresponding to an apparent extent of reaction) at zero time. Finally the actual values of rate constants obtained by the various methods are considered.

Reproducibility of Rate Constants.—Rate constants obtained by the spectral method at 25 and at 0 °C are shown in Tables 1 and 2 respectively. Reproducibility is generally within 3% and only one ketone has a reproducibility of worse than 7% (3,3,5,5-tetramethylcyclohexanone, 11%). This order of reproducibility is similar to results reported by Rickborn and Wuesthoff, both the potentiometric and chromatographic methods giving reproducibilities generally within 3% but occasionally as high as 8·8% (potentiometric) and 12·2% (g.l.c.) respectively.[3] Results quoted by Brown *et al.*[5] for the iodate titration method appear to be consistently within 2%.

Effect of Concentration.—Tables 1 and 2 also show the

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[1] D. C. Wigfield and D. J. Phelps, *Chem. Comm.*, 1970, 1152.

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[4] D. A. Lyttle, E. H. Jensen, and W. A. Struck, *Analyt. Chem.*, 1952, **24**, 1843.

[5] H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron*, 1957, **1**, 214.

[6] H. C. Brown and K. Ichikawa, *Tetrahedron*, 1957, **1**, 221.

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TABLE 1

Kinetic data for the reduction of ketones by sodium borohydride in propan-2-ol at 25 °C

Ketone	10^2[Ketone]/M	10^2[Hydride]/M	10^4k / l mol^{-1} s^{-1}	Correlation coefficient
Cyclohexanone	4·44	0·93	788	0·9998
	4·81	0·93	722	0·9999
	6·02	0·93	731	0·9997
	5·27	1·05	815	0·9999
	5·11	1·05	768	0·9999
		Average	765 ± 31 [b]	
3-Methylcyclohexanone	4·46	1·05	620	0·9998
	2·37	0·93	608	0·9999
	4·31	1·05	588	0·9986
		Average	605 ± 12	
2-Methylcyclohexanone	4·26	1·71	144	0·9998
	4·69	1·71	154	0·9995
	3·94	0·85	149	0·9998
	5·43	1·71	148	0·9999
		Average	149 ± 3	
3,3,5-Trimethylcyclohexanone	4·13	0·66	22·2	0·9984
	3·44	1·71	22·1	0·9995
	3·51	1·71	21·2	0·9997
		Average	21·8 ± 0·4	
3,3,5,5-Tetramethylcyclohexanone	2·36	1·71	2·33	0·9988
	3·45	0·93	1·83	0·9942
	3·51	0·93	1·88	0·9771
	4·05	0·93	1·63	0·9866
		Average	1·92 ± 0·21	
Acetone	3·34	1·71	82·9	0·9999
	3·37	1·71	85·9	0·9999
	8·32	1·71	76·2	0·9997
	3·55	0·66	83·7	0·9998
	3·45	0·66	82·3	0·9991
	5·25	0·66	75·6	0·9997
		Average	81·1 ± 3·5	
Acetophenone [a]	0·16	1·71	17·3	0·9999
	0·16	1·71	16·7	0·9999
	0·17	1·71	16·1	0·9999
		Average	16·7 ± 0·4	

[a] The ketone concentration for acetophenone is much lower to accommodate the higher extinction coefficient of this ketone. Kinetics of reductions of such conjugated ketones have previously been measured spectrophotometrically (ref. 9). [b] Limits quoted in all Tables are the mean deviations from the mean.

TABLE 2

Kinetic data for the reduction of ketones by sodium borohydride in propan-2-ol at 0 °C

Ketone	10^2[Ketone]/M	10^4k / l mol^{-1} s^{-1}	y Intercept (% reaction)	Correlation coefficient
Cyclohexanone [a]	2·54	264	0	0·9993
	3·52	246	3σ (<1%)	0·9993
	3·48	260	4σ (<1%)	0·9991
	2·88	264	0	0·9994
	2·87	270	3σ (<1%)	0·9987
	Average	261 ± 5		
3-Methylcyclohexanone [b]	4·22	168	0	0·9992
	2·94	186	0	0·9994
	Average	177 ± 9		
2-Methylcyclohexanone [a]	3·69	38·1	0	0·9989
	2·51	41·5	0	0·9994
	3·42	37·4	3σ (<1%)	0·9998
	Average	39·0 ± 1·3		
3,3,5-Trimethylcyclohexanone [a]	2·81	4·76	0	0·9986
	2·87	5·21	0	0·9989
	2·42	4·31	0	0·9992
	Average	4·76 ± 0·30		
3,3,5,5-Tetramethylcyclohexanone [a]	2·48	0·31	0	0·9630 [c]
	2·57	0·31	0	0·9588 [c]
	Average	0·31		

[a] $NaBH_4$ concentration 0·0103M. [b] $NaBH_4$ concentration 0·0091M. [c] This rate is approaching the lower limit that can be measured by the spectral method. The change in O.D. with time is very small and thus the plots tend to be stepwise, giving rise to apparently poor correlation coefficients.

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[9] G. G. Smith and R. P. Bayer, *Tetrahedron*, 1962, **18**, 323.

concentration ranges over which kinetic measurements were taken. The [ketone] : [hydride] ratio was varied between 1·38 and 7·95 with the reproducibilities indicated above. These results are in agreement with those of Brown and his co-workers[5,6] who have established the non-variance of rate constants over a considerably wider range by the titration method, thus verifying that the reduction is a true second-order process. A systematic study for the potentiometric and chromatographic methods has not been reported although deviations of a few per cent. have been noted when the [ketone] : [hydride] ratios are varied from the stoicheiometric ratio.[3]

TABLE 3

Comparison of rate constants obtained by the spectral method at 25 °C with those from the iodate titration method

Ketone	10^4k/l mol^{-1} s^{-1} Spectral	Titration	$k_{\text{spect}}/k_{\text{tit}}$
Acetone	81·1 ± 3·5	63·0[a]	1·29
Acetophenone	16·7 ± 0·4	13·9[a]	1·20
Cyclohexanone	765 ± 31	565[b]	1·35
2-Methylcyclohexanone	149 ± 3	120[c]	1·24

[a] From ref. 5. [b] From ref. 6. [c] From ref. 7.

Correlation Coefficients.—For individual runs, the spectral method gives highly satisfactory second-order plots. Correlation coefficients (see Tables 1 and 2) are typically around 0·999. No corresponding data on the other three methods are available.

Intercepts.—The obvious major drawback of the iodate titration method[5] pointed out by Rickborn and Wuesthoff[3] is that it gives rise to non-zero intercepts at zero time, sometimes corresponding to as much as 7% reaction. In contrast to this, the potentiometric method gave intercepts equal to zero within experimental error (taken to be two standard deviations). The magnitudes of the intercepts obtained by following the reductions by the spectral method are in Table 2, and demonstrate that for slower reductions, the intercepts are also zero within two standard deviations. For the faster reactions, in the absence of a rapid mixing system, there is some ambiguity about the point of zero time, which does give rise to small intercepts, in some cases as high as 4σ. However, even in these cases, the intercept corresponds to less than 1% reaction and does not appear to be an inherent shortcoming of the method.

Values of the Rate Constants.—Reductions of ketones in our work[1,2] have generally been performed at 25 °C, and these results (Table 1) may be compared (Table 3) with those of Brown and his co-workers[5-7] using the iodate titration method. The spectral method gives rate constants consistently about 30% larger than those obtained titrimetrically. This result is in agreement with the conclusion of Rickborn and Wuesthoff that the iodate titration method gives measurably low values of rate constants. The results reported for the potentiometric and g.l.c. methods[3] all refer to 0 °C and hence reductions with use of the spectral method were performed at 0 °C (Table 2) for comparison (Table 4) with these other methods. There is good agreement between the rate constants obtained by the three methods, none giving consistently higher or lower values than another.

TABLE 4

Comparison of rate constants obtained by the spectral method at 0 °C with those from the potentiometric and chromatographic methods

Ketone	10^4k/l mol^{-1} s^{-1} Spectral	Potentiometric[a]	Chromatographic[a]	$k_{\text{spect}}/k_{\text{pot}}$	$k_{\text{spect}}/k_{\text{chrom}}$
Cyclohexanone	261 ± 5	235 ± 9		1·11	
3-Methylcyclohexanone	177 ± 9	179 ± 3	217 ± 19	0·99	0·82
2-Methylcyclohexanone	39·0 ± 1·3	42·1 ± 0·6	39·9 ± 0·6	0·93	0·98
3,3,5-Trimethylcyclohexanone	4·76 ± 0·30	4·70 ± 0·09	4·55 ± 0·4	1·01	1·07
3,3,5,5-Tetramethylcyclohexanone	0·31 ± 0·00	0·34 ± 0·03		0·91	

[a] From ref. 3.

TABLE 5

Comparison of kinetic methods for the reduction of ketones by sodium borohydride

Criteria	Method Titration	Potentiometric	Chromatographic	Spectral
(i) Rate constant reproducibility	<2%	<9%	<12·2%	<11%
(ii) [Ketone] : [Hydride] ratio range	1·99—18·60			1·38—7·95
(iii) Typical correlation for individual runs				0·999
(iv) Intercepts	Up to 7% reaction	<2σ		⩽4σ (1% reaction)
(v) Average relative rates (relative to k_{spect} = 1·00)	0·79	0·99	0·96	1·00

Conclusions.—Table 5 summarizes the results. From the point of view of criteria (i)—(iv), the spectral method compares favourably with any of the others in particular not giving the non-zero intercepts characteristic of the iodate titration method. Further, the average deviations of the potentiometric and chromatographic rate constants relative to the spectral rate constants are satisfyingly small. These results suggest that the spectral method is valid for measurement of the kinetics of borohydride reduction of ketones; they also add weight to the view[3] that the iodate titration method gives rise to significantly low values of rate constants.

EXPERIMENTAL

The details of the kinetic method have been described.[2] The data were treated by plotting I [see equation (1)] against t where a = initial ketone concentration, b = initial borohydride concentration, and x = concentration of ketone remaining at time t. The slopes, equal to $k(a - 4b)/2{\cdot}303$, where k is the second-order rate constant,* the intercepts, and the standard deviations were obtained from a least-squares programme on a Xerox Sigma 7 computer.

For calculation of the relationship between the extent of reaction and the magnitude of the intercept, I, x was extracted from the relationship (1) and the extent of reaction put equal to $100(x/a)$ %.

$$I = \log_{10}\frac{4b}{a}\frac{(a-x)}{(4b-x)} \qquad (1)$$

For measurement of kinetics at 0 °C, the entire kinetic apparatus was placed in a cold room at 10 °C and a RTE-3 cooling circulator, Neslab Instruments, Inc., used to maintain the temperature at $0 \pm 0{\cdot}5$ °C.

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* In common with previous practice (*e.g.*, refs. 2 and 3), this rate constant refers to the rate of disappearance of borohydride, despite the fact that our measurements are based on ketone concentration, in order that direct comparisons of rate constants obtained by different methods may be made. Clearly the two rate constants differ by a factor of 4.