Kinetics of Bromination of 1-Hetera-4-cyclohexanones by *N*-Bromosaccharin

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The kinetics of bromination of some substituted 4-piperidones and 4-selenanones by *N*-bromosaccharin in the presence of perchloric acid in aqueous acetic acid have been investigated. The bromination is first order in both substrate and H_3O^+ and zero order in NBSA. A plausible mechanism based on these observations is proposed. The effects of the various substituents on the rates of bromination have been rationalized on the basis of their inductive and steric effects. The effect of solvent polarity on the rate has also been studied.

N-Bromosaccharin (NBSA) as an oxidant has been the subject of several publications.[1-5] However, this bromination study is aimed at investigating the kinetics of bromination of various substituted 1-heteracyclohexan-4-ones with NBSA.

Results and Discussion

The kinetics of bromination of 1-heteracyclohexan-4-ones (**1**)—(**15**) by NBSA in aqueous acetic acid in the presence of perchloric acid have been investigated under pseudo-zero-order conditions, with the substrate in large excess, and the results are presented in Tables 1 and 2. The first-order dependence on the rate on substrate concentration can be seen from Table 3. Table 2 also records the first-order rate constants, obtained by the division of the psuedo-zero-order rate constants by the concentration of the substrate. The data presented in Table 4 indicate that the reaction is acid catalysed and that the order with respect to acid is unity.

The sensitivity of the reaction to solvent polarity was studied by changing the composition of the medium, and the results are recorded in Table 5. The rate was observed to decrease with increasing solvent polarity, indicating that the charge density in the transition state is less than that in the reactants. Activation parameters, presented in Tables 6 and 7, were obtained by running the reaction at several temperatures.

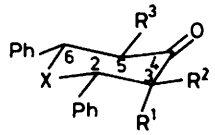
Mechanism and Rate Law.—In all the cases investigated, the reaction was found to follow zero-order kinetics with respect to NBSA. This observation, coupled with the fact that the reaction is first order in both substrate and H^+, led us to propose the mechanism in the Scheme for the reaction. The rate law for this

$$\text{Rate} = \frac{-\text{d}\,[\text{NBSA}]}{\text{d}t} = k_s K[\text{Substrate}][\text{H}^+] \quad (1)$$

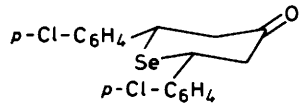
mechanism is given in equation (1). With a large excess of substrate, its concentration thus remaining virtually constant, and the concentration of H^+ remaining constant during the entire run, the rate law reduces to equation (2).

$$\text{Rate} = k_o \quad (2)$$
$$\text{Where } k_o = k_s K\,[\text{Substrate}][\text{H}^+]$$

^{1}H N.m.r. analysis of the product obtained from (**7**) indicates that the incoming bromine has become attached to the unsubstituted α-carbon and occupied the equatorial position. A similar analysis of the product from (**10**) shows the bromine in



	X	R^1	R^2	R^3
(**1**)	NH	H	Me	H
(**2**)	NH	H	Et	H
(**3**)	NH	H	Pr^i	H
(**4**)	NH	H	Me	Me
(**5**)	NH	H	Et	Et
(**6**)	NH	Me	Me	H
(**7**)	NCH_3	H	Me	H
(**8**)	NCH_3	H	Et	H
(**9**)	NCH_3	H	Pr^i	H
(**10**)	NCH_3	H	Me	Me
(**11**)	NCH_3	H	Et	Et
(**12**)	NCH_3	Me	Me	H
(**13**)	Se	H	H	H
(**14**)	Se	H	Me	H



(**15**)

Table 1. Evaluation of the zero-order rate constant for substrate (**7**)[a]

Time/min	$[\text{NBSA}]_o - [\text{NBSA}]_t$ / 10^{-4}M	
0	0	$k_o = 51.4 \times 10^{-6}$ mol l^{-1} min^{-1}
2	1.05	
4	2.05	
7	3.60	
10	5.15	
14	7.21	

[a] [Substrate] = 8.94mM; [NBSA] = 0.964mM; $[HClO_4]$ = 1.74M; solvent HOAc–H_2O (80:20 v/v); T = 50 °C.

Table 2. Pseudo-zero-order and first-order rate constants for the bromination of 1-heteracyclohexan-4-ones by NBSA[a]

Comp.	10^6k_o/mol l^{-1} min^{-1}	10^4k_1/min^{-1}
(1)	7.23	8.09
(2)	8.02	8.97
(3)	4.93	5.51
(4)	0.64	0.71
(5)	1.57	1.75
(6)	3.39	3.79
(7)	51.35	57.44
(8)	59.50	66.55
(9)	29.46	32.95
(10)	3.97	4.44
(11)	17.84	19.96
(12)	21.30	23.83
(13)	18.55	20.75
(14)	5.37	6.01
(15)	4.84	5.41

[a] See footnote *a* to Table 1.

Table 3. Dependence of rate on substrate concentration substrate (7)[a]

10^3[substrate]/ mol l^{-1}	10^6k_o/mol l^{-1} min^{-1}	10^3k_1/min^{-1}
2.31	13.31	57.64
5.81	33.28	57.28
8.94	51.35	57.44
11.53	66.31	57.51

[a] Except for [substrate], data as in footnote *a* to Table 1.

Table 4. Effect of varying acid concentration on the reaction rate substrate (7)[a]

10^2[$HClO_4$]/mol l^{-1}	10^6k_o/mol l^{-1} min^{-1}
25.60	6.96
51.10	12.69
102.10	29.41

[a] [Substrate] = 10.45mM; [$HClO_4$] given above, other data as in footnote *a* to Table 1.

Table 5. Dependence of rate on the polarity of the medium substrate (8)[a]

HOAc–H_2O (v/v)	10^6k_o/mol l^{-1} min^{-1}
50—50	27.95
60—40	34.94
70—30	43.14
80—20	63.51
90—10	73.50

[a] [substrate] = 10.54mM; solvent ratio given above; other data as in footnote *a* to Table 1.

Table 6. Evaluation of activation parameters for substrate (7)[a,b]

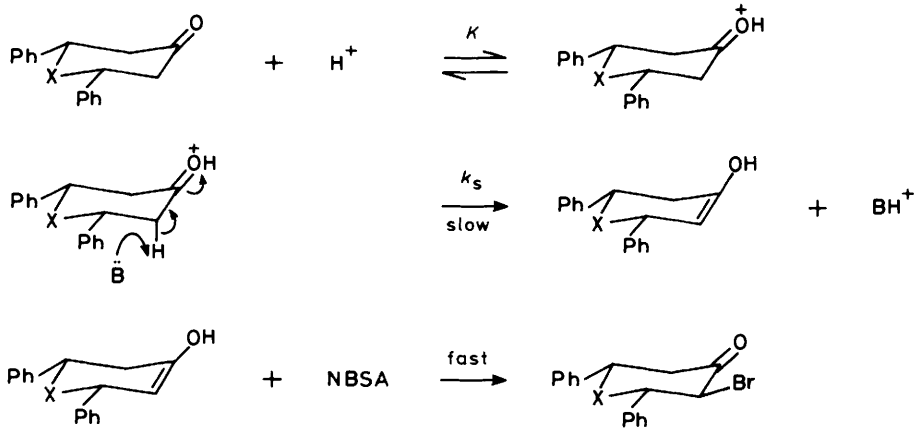
T/K	10^3k_1/min^{-1}	ln (k_1/T)	10^3 ($1/T$)
313	2.23	−11.80	3.195
318	3.74	−11.35	3.145
323	5.74	−10.91	3.096
328	9.12	−10.49	3.049
333	13.96	−10.08	3.003

[a] Plot of ln (k_1/T) *versus* ($1/T$) is linear with the regression coefficient −0.99. From the intercept, $\Delta S^{\ddagger}$ was evaluated as −57.61 J mol^{-1} K^{-1}. From the slope, $\Delta H^{\ddagger}$ was evaluated as 74.50 K J mol^{-1}. [b] See footnote *a* to Table 1.

Table 7. Activation parameters for the bromination of *N*-methyl-4-piperidones by NBSA in aqueous acetic acid (80% v/v) in the presence of $HClO_4$ (1.74M)

Piperidone	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
(7)	74.50	−57.61
(8)	72.24	−58.50
(9)	78.15	−60.08
(10)	81.35	−61.21
(11)	79.04	−61.57
(12)	78.75	−59.32

Structure and Reactivity.—All the compounds investigated have been shown from their ^{1}H- and ^{13}C-n.m.r. studies to exist in the chair conformation with the phenyl and alkyl substituents



Scheme

the axial position of the α-carbon. As compounds (7) and (10) may be considered typical members of groups of compounds bearing one and two equatorial α-substituents, respectively, the conclusions drawn in these two cases may be extended to other members of their respective groups.

occupying the least strained equatorial positions.[6–8] In compounds (6) and (12), however, one of the methyl groups must necessarily be placed in the axial position.

The effect of the alkyl substituents on the rates of bromination in the N–Me series parallels their effects in the N–H series. A

combination of both steric and electronic factors seems to be responsible for the observed trend in the rates. The slight increase in the rate in going from (**1**) to (**2**) and from (**7**) to (**8**) is probably due to the inductive effect of the distant alkyl substituent on the rate of proton abstraction from the unsubstituted α-carbon by a general base in the enol formation step. As the methyl group is more electron releasing than the ethyl group,[9] it discourages the abstraction of a proton. The fact that the alkyl substituent is considerably separated from the proton abstraction site accounts for the small observed rate difference between the methyl- and ethyl-substituted compounds.

The extent to which the presence of an alkyl substituent near the site of proton abstraction can reduce the rate of bromination can be gauged by comparing the rates of (**1**), (**2**), (**7**), and (**8**) with those of (**4**), (**5**), (**10**), and (**11**), respectively. The larger reduction observed is understandable on the basis of the proximity of the electron-releasing alkyl group to the site of proton abstraction and the steric interaction of this group with the approaching basic species. Once again a comparison between the methyl- and the ethyl-substituent effect reveals that the former is more electron releasing and hence more retarding. This is in spite of the fact that a methyl group is less bulky and hence less retarding sterically than the ethyl group.

Consideration of the fact that the replacement of a more electron-releasing methyl group by a less electron-releasing ethyl group enhances the rate would lead one to anticipate a further enhancement of rate when an isopropyl group is introduced in place of the methyl group.[9] On the contrary, a diminution of rate has been observed in both the N–H as well as the N–Me series. Compare the rate of (**3**) with that of (**1**) or (**2**) and the rate of (**9**) with that of (**7**) or (**8**). It is probable that in the case of the bulky isopropyl group, the steric factor outweighs the electronic factor and the isopropyl group hinders the approach of the base in the rate-limiting enolization step.

The reduced rates of (**6**) and (**12**) when compared with those of (**1**) and (**7**), respectively, can be attributed to the inductive effect of the second methyl substituent. The inductive effect also explains why (**14**) reacts more slowly than (**13**).

In all the cases investigated, an N–Me compound was observed to react faster than the corresponding N–H compound. This may be owing to the fact that, unlike in N–H compounds, in N–Me compounds the lone pair preferentially occupies the sterically more crowded axial position.[10] The 1,3-interaction between this lone pair and the axial hydrogens at positions 3 and 5 could enhance the ground-state energy of the reactant and consequently lead to a lowering of activation energy.

Experimental

Materials.—The 1-heteracyclohexan-4-ones used in the present investigation were prepared following literature procedure.[6,11,12] *N*-Bromosaccharin was prepared by treating saccharin with bromine in alkaline medium.[1]

Acetic acid (AnalaR; B.D.H.) was refluxed over CrO_3 and used as solvent.[13,14] Other chemicals used were of reagent grade (B.D.H.).

Kinetic Measurements.—Pseudo-zero-order conditions were maintained by taking a large excess of substrate. In order to avoid photocatalysis, reactions were run in the dark. Solutions of the substrate and NBSA were separately thermostatted at 50 ± 0.05 °C for 30 min before mixing. The rate was followed by taking aliquots (2 ml) of the reaction mixture, pouring into a known excess of standard KI solution and titrating the liberated iodine against standard thiosulphate solution using starch as indicator. The reactions were followed to at least up to 70% conversion of NBSA. The results were reproducible to within ±5%.

To obtain the activation parameters, the reactions were run at several temperatures. Following the Eyring equation (3), ln (k_1/T) was plotted against $(1/T)$ and the enthalpy of activation $(\Delta H^{\ddagger})$ and entropy of activation $(\Delta S^{\ddagger})$ were evaluated from the slope and intercept, respectively, of the straight-line plot.

$$\ln (k_1/T) = \ln (k/\mathrm{h}) + \Delta S^{\ddagger}/R - \Delta H^{\ddagger}/R\,(1/T) \quad (3)$$

Product Analysis.—The bromination of piperidone by NBSA resulted in the formation of the corresponding α-bromo derivative as the product. A solution (50 ml) containing piperidone (0.5 mol), NBSA (0.05 mol), and perchloric acid (3.5M) in aqueous acetic acid (80% v/v) was heated to 80—90 °C for 2 h, cooled, and the acid neutralized by the addition of dilute ammonia. Water (50 ml) was then added and the insoluble saccharin was filtered off. The filtrate was extracted with ether (3 × 50 ml) and the combined ether extracts were dried (Na_2SO_4) and evaporated. The residue was dissolved in the minimum amount of benzene and chromatographed over a column of neutral alumina. The bromopiperidone isolated (yield *ca.* 15%) was analysed by ^{1}H n.m.r. spectroscopy. The product from (**7**) gave signals at δ 0.85 (3 H, d, *J* 7 Hz, 3-Me), 1.80 (s, 3 H, N-Me), 3.00 (m, 1 H, 3-H), 3.80 (d, 1 H, *J* 11 Hz, 2-H), 4.00 (d, 1 H, *J* 10 Hz, 6-H), 5.6 (d, 1 H, *J* 10 Hz, 5-H), and 7.3—7.7 (m, 10 H, 2- and 6-Ph). The product from (**10**) gave signals at δ 0.85 (d, 3 H, *J* 7 Hz, 3-Me), 1.50 (s, 3 H, 5-Me), 1.80 (s, 3 H, N-Me), 3.00 (m, 1 H, 3-H), 3.80 (m, 2 H, 2- and 6-H), and 7.3—7.7 (m, 10 H, 2- and 6-Ph).

Acknowledgements

We thank Professor D. K. P. Varadarajan, Principal, P.S.G. College of Arts and Science, Coimbatore and Dr. G. R. Damodaran and Mr. G. Varadaraj, M.P., Managing Trustees, P.S.G. Institutions, for their constant encouragement and the facilities provided. Thanks are also due to Dr. Sethu Rao for help.

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Received 13*th August* 1985; *Paper* 5/1414