Reactivities of Variously Substituted 4-Heteracyclohexanones in the Formation of Oximes [1]

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The rates of oxime formation of 41 heterocyclic ketones have been measured at 5 °C in aqueous alcoholic solution buffered at pH 6.85. The data indicate an overall second-order reaction, first order each in ketone and hydroxylamine. In all cases investigated the reaction appears to be irreversible under the experimental conditions employed. Increased steric retardation is observed as steric crowding around the carbonyl function increases, suggesting that rate-determining attack of the hydroxylamine on the carbonyl group takes place. The rates of oxime formation for 4-piperidones, oxan-4-ones, thian-4-ones, the corresponding 1,1-dioxides, and selenan-4-ones differ significantly.

Although addition of nitrogen nucleophiles to carbonyl compounds has been studied extensively,[2-6] work on the addition of hydroxylamine to saturated heterocyclic ketones is conspicuously lacking. In the present investigation rates of oxime formation of variously substituted 4-heteracyclohexanones (1)—(41) were followed with a view to gaining knowledge about their conformation and to studying the effect of the heteroatom on the reactivity of the carbonyl group.

Results

For all the compounds investigated, there was found to be no measurable hydrolysis. The reaction followed a second-order rate law, first order each in ketone and hydroxylamine. This has been further confirmed by using pseudo-first-order conditions, taking a large excess of ketone. The second-order rate constants for various ketones are given in Table 1. The pseudo-first-order rate constants for compound (16) are presented in Table 2 and these, as might be expected, are proportional to the ketone concentration.

The influence of ionic strength on the rate of oxime formation has been studied by running the reaction in the presence of known amounts of added potassium chloride and the results are reported in Table 3.

Table 1. Second-order rate constants of oxime formation of various heterocyclic ketones. Solvent 80% ethanol–20% water (v/v); pH 6.85; temperature 5 °C; *I* 0.1M

Compound	10^2k_2/ l mol^{-1} s^{-1}	Compound	10^2k_2/ l mol^{-1} s^{-1}
(1)	82.60	(21)	34.76
(2)	88.02	(22)	26.79
(3)	59.59	(23)	1.25
(4)	8.58	(24)	0.18
(5)	6.09	(25)	0.35
(6)	36.55	(26)	0.17
(7)	36.67	(27)	0.043
(8)	34.62	(28)	0.067
(9)	6.58	(29)	0.078
(10)	0.11	(30)	0.080
(11)	1.79	(31)	0.078
(12)	35.65	(32)	100.17
(13)	35.70	(33)	100.22
(14)	8.03	(34)	45.13
(15)	33.72	(35)	34.48
(16)	5.73	(36)	56.65
(17)	6.87	(37)	56.24
(18)	2.85	(38)	110.57
(19)	25.02	(39)	36.57
(20)	2.63	(40)	2.46
		(41)	0.81

Table 2. Dependence of rate on concentration of *r*-2,*c*-6-diphenyl-*t*-3-ethylthian-4-one (16) (S). Solvent 80% ethanol–20% water (v/v); pH 6.85; temperature 5 °C; [NH_2OH] 18.31 × 10^{-4}M; *I* 0.075M

10^3[S]/mol l^{-1}	10^4k_1/s^{-1}	10^2k_2/l mol^{-1} s^{-1}
17.84	7.37	4.13
21.94	8.97	4.09
26.19	10.94	4.18
32.59	13.27	4.07
		Mean = 4.12 ± 0.05

Discussion

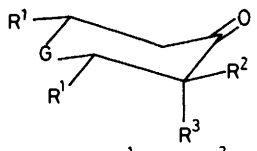
The absence of a salt effect on the rate of oxime formation (Table 3) indicates that the rate-determining step may be one between uncharged molecules or between an ion and an uncharged molecule. Apart from proton transfer reactions, oxime formation is known to take place in two steps (1) and (2).[2,4,5] Step (1), the addition of free hydroxylamine to the carbonyl group, is subject to very weak specific acid catalysis[7,8] while the second step, the dehydration of the addition complex, is subject to both general [4,9] and specific [9] acid catalysis.

The rate-determining step of oxime formation is pH dependent. Neutral pH seems to favour step (2) and acid pH step (1) as the rate-limiting steps.[4,5,9] There is a transition in the rate-limiting step from (2) to (1) as the pH is lowered. This transition can also be effected by structural changes in the carbonyl compound and changes in the nucleophilicity of the nitrogen species.

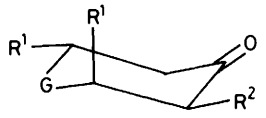
The carbinolamine derived from ketone and hydroxylamine is a tertiary alcohol and hence should undergo a faster acid catalysed dehydration than the carbinolamine obtained from an aldehyde. For ketones, therefore, the attack of hydroxylamine becomes rate determining even at higher pH. Earlier investigations [2,4,9-12] confirm this view.

It has been observed that the rates of oximation of ketones (3) and (15) are higher (*ca.* 12 and 5.5 times, respectively) than those of semicarbazone formation under identical conditions (pH 6.85; 5 °C). Since hydroxylamine is a stronger nucleophile than semicarbazide and since an increase in nucleophilicity should increase the rate of reaction if step (1) is rate limiting,

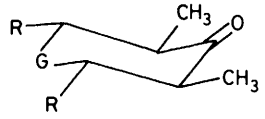
	G	R
(1)	NMe	Ph
(2)	O	Ph
(3)	S	Ph
(4)	SO_2	Ph
(5)	SO_2	p-ClC_6H_4
(6)	Se	Ph
(7)	Se	p-MeC_6H_4



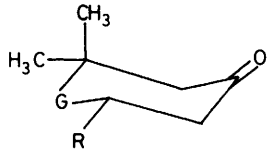
	G	R^1	R^2	R^3
(8)	NMe	Ph	Me	H
(9)	NMe	Ph	Et	H
(10)	NMe	Ph	Pr^i	H
(11)	NMe	Ph	Me	Me
(12)	O	Ph	Me	H
(13)	O	p-$MeOC_6H_4$	Me	H
(14)	O	Ph	Et	H
(15)	S	Ph	Me	H
(16)	S	Ph	Et	H
(17)	SO_2	Ph	Me	H
(18)	SO_2	Ph	Et	H
(19)	Se	Ph	Me	H
(20)	Se	Ph	Et	H



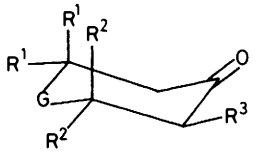
	G	R^1	R^2
(21)	O	Ph	H
(22)	S	Ph	H
(23)	S	Ph	Me
(24)	S	Ph	Et
(25)	SO_2	Ph	H
(26)	SO_2	Ph	Me
(27)	SO_2	Ph	Et



	G	R
(28)	NMe	Ph
(29)	O	Ph
(30)	O	p-MeC_6H_4
(31)	O	p-$MeOC_6H_4$



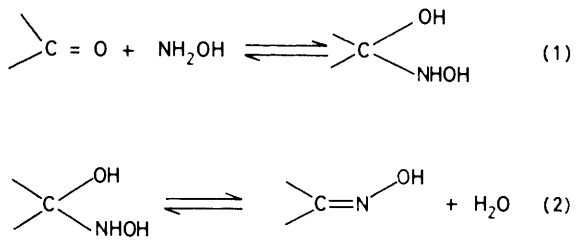
	G	R
(32)	S	Ph
(33)	S	p-ClC_6H_4
(34)	SO_2	Ph
(35)	SO_2	p-ClC_6H_4
(36)	Se	Ph
(37)	Se	p-ClC_6H_4

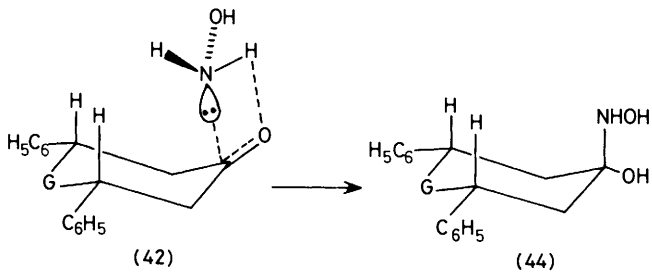


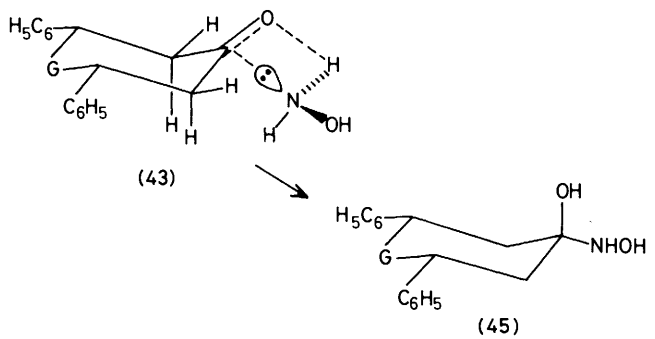
	G	R^1	R^2	R^3
(38)	S	H	Me	H
(39)	S	Me	Me	H
(40)	S	H	H	Pr^i
(41)	SO_2	H	H	Pr^i

Table 3. Effect of varying ionic strength on the reaction rate of *r*-2,*c*-6-diphenyl-*t*-3-ethylthian-4-one (16). Solvent 80% ethanol–20% water (v/v); pH 6.85; temperature 5 °C

10^3I/mol l^{-1}	10^2k_2/l mol^{-1} s^{-1}
61.62	5.76
70.40	5.72
80.62	5.73
91.50	5.76
100.00	5.71





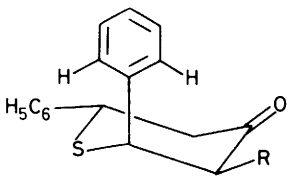


the above observation suggests that for ketones the attack of nucleophile is rate determining.

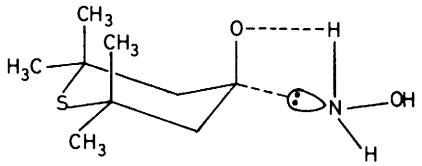
The configurations and conformations of the heterocyclic ketones have been assigned by ^1H and ^{13}C n.m.r. spectra.[13–16] Two transition states (42) and (43) are possible for the addition of hydroxylamine to a six-membered heterocyclic ketone which is anchored in a single chair conformation.

In (42) the hydroxylamine approaches the ketone from the axial side and in (43) the approach is from equatorial side. The transition state (42) should lead to a carbinolamine (44) with an equatorial hydroxy-group and (43) to a carbinolamine (45) with an axial hydroxy-group. A Courtauld scale model reveals greater steric hindrance to the axial approach of the hydroxylamine. Hence, hydroxylamine may be expected to attack preferentially from the equatorial side [transition state (43)]. The carbinolamine (44) or (45) will develop non-bonded steric interactions of the newly formed OH and NHOH groups with synaxial hydrogens and also with adjacent hydrogens. The non-bonded steric interactions will be even more severe if adjacent hydrogens are replaced by a bulky substituent. Such interactions will decelerate the addition step but accelerate the dehydration step.

The results of the present investigation support this view. Introduction of an alkyl substituent at the 3-position (α to the carbonyl function) decreases the rate of oxime-formation. Thus *r*-2,*c*-6-diphenyl-*t*-3,*N*-dimethyl-4-piperidone (8), *r*-2,*c*-6-diphenyl-*t*-3-methyloxan-4-one (12), *r*-2,*c*-6-diphenyl-*t*-3-methylthian-4-one (15), and *r*-2,*c*-6-diphenyl-*t*-3-methylselenan-4-one (19) react with hydroxylamine at a slower



(23) R = Me
(24) R = Et



(46)

rate than the corresponding ' parent ' 4-hetera-3,5-diarylcyclohexanones (1)—(3) and (6), respectively. Also, an increase in the bulkiness of the α-substituent, as expected, further lowers the rate of oximation. Thus compound (8) reacts faster than (9) which in turn reacts faster than (10). A similar trend is found for the oxygen, sulphur, and selenium analogues.

Introduction of a second alkyl substituent on the same α-carbon also lowers the rate. Thus *r*-2,*c*-6-diphenyl-*c*-3,*t*-3,N-trimethyl-4-piperidone (11) reacts *ca.* 19 times slower than *r*-2,*c*-6-diphenyl-*t*-3,*N*-dimethyl-4-piperidone (8).

A remarkable decrease in rate is observed when alkyl substituents are introduced at the 3,5-positions (α,α′ to the carbonyl function). For example, piperidone (28) reacts 1 200 times slower than the corresponding ' parent ' piperidone (1). Such a striking retardation in rate indicates that there should be greater steric crowding in the transition state than in the ground state which is possible only when the addition step is rate determining. A comparison of rate constants of oximation for *r*-2,*c*-6-diphenyl- (29) *r*-2,*c*-6-di-*p*-tolyl- (30), and *r*-2,*c*-6-bis-*p*-methoxyphenyl-*t*-3,*t*-5-dimethyloxan-4-one (31) indicates that the presence of a substituent in the *para*-position of the phenyl ring does not affect the rate of oximation.

A β-axial group is also able to retard the rate of oxime formation appreciably because of the greater steric requirements of the axial phenyl group. For example *r*-2,*t*-6-diphenyl- (22) *r*-2,*t*-6-diphenyl-*c*-3-methyl- (23), and *r*-2,*t*-6-diphenyl-*c*-3-ethylthian-4-one (24) are less reactive than the corresponding all-equatorial thian-4-ones (3), (15), and (16), respectively. The conformations and configurations of (23) and (24) have been proved by *X*-ray studies.[14] The *X*-ray data [14] indicate that one *ortho*-hydrogen atom in the axial phenyl is in close proximity to the carbonyl carbon in the crystalline state.

2,2,6,6-Tetramethylthian-4-one (39) reacts with hydroxylamine approximately three times slower than 2,2-dimethylthian-4-one (38). In the case of 2,2,6,6-tetramethylthian-4-one (39) the forming hydroxy-group in the transition state (46) develops an unfavourable interaction with two synaxial methyl groups and this would explain the slower rate for thianone (39).

The rate data in Table 1 indicate that the sulphone ketones react with hydroxylamine very much slower than that of sulphide ketones. The behaviour of sulphone ketones cannot be explained on the basis of the electron-withdrawing inductive effect of the sulphonyl group. For a rate-determining addition of hydroxylamine to the carbonyl group, the rate of sulphone ketone is expected to be higher than the rate of sulphide, since the sulphonyl group increases the positive charge on the carbonyl carbon. Although the sulphonyl group itself is susceptible to nucleophilic attack under certain conditions, in the present investigation no reaction was observed when the oxime of thian-4-one 1,1-dioxide is treated with hydroxylamine. However, it is likely that the presence of the sulphonyl group diverts some of the hydroxylamine molecules towards itself and thereby lowers the ' effective concentration ' of the nucleophile available for attack on carbonyl carbon. The lowered reactivity of sulphonyl ketones compared with that of sulphide ketones might probably be due to this factor.

The effect of a change in the heteroatom on the rate of oxime formation may be seen from Table 1. Examination of the data in Table 1 reveals that the heteroatom effect is in the order O > NCH_3 > S > Se. The differences in rate may be due to a combination of the polar effects of the heteroatom and the intrinsic conformational differences that exist due to different bond parameters of the heteroatom. The ^{13}C n.m.r. spectra of variously substituted 4-heteracyclohexanones [17] also confirm the polar effect of the heteroatom (γ-effect) on the carbonyl carbon. In the heterocyclic ketones flattening of the heterocyclic ring occurs to a different extent in differently substituted cyclohexanone. The resulting subtle differences in shape of these 4-hetera-3,5-diarylcyclohexanones might, then, in turn affect the reactivity of the heterocyclic ketones.

Experimental

Compounds (1)—(41) were prepared as reported.[13-16]

Reagents.—Ethanol used for the kinetic study was purified by the literature method.[18] The reaction medium, containing ethanol (80% v/v), was prepared by diluting 0.25M-acetic acid (60 ml) and 0.25M-sodium acetate (140 ml) to 1 l with ethanol in a volumetric flask and its pH was found to be 6.85 ± 0.05 (solution A).

Hydroxylamine hydrochloride (10 g) was purified by dissolving in a minimum amount of water (20 ml) and saturating with hydrogen chloride. Three such recrystallisations yielded a product which was dried *in vacuo* ($CaCl_2$–NaOH). The hydroxylamine solution was prepared by dissolving a weighed quantity (0.02M) of hydroxylamine hydrochloride in ethanol in a standard flask. The free hydrogen chloride in hydroxylamine solution was neutralised by adding a calculated amount of standard sodium hydroxide and acetic acid–acetate buffer was added with the proviso the final made up solution should contain 80% (v/v) ethanol and have pH 6.85 ± 0.05, similar to the reaction medium (solution B). The hydroxylamine solution was prepared, estimated, and used on the same day. pH Measurements were made on Elico pH meter model LI-10.

Kinetic Measurements.—The titrimetric method used to follow the reaction was the same as that used for studying the kinetics of semicarbazone formation.[19,20] The alcohol and hydroxylamine solutions A and B were equilibrated at 5.00 °C in an MLW ultracryostat, type MK 70, with an accuracy of ± 0.02 °C. A weighed quantity of the ketone (0.002—0.004M) was dissolved in the cold alcohol solution A (20 ml) and kept at 5.00 °C. The ionic strength of the solution was maintained constant by the addition of potassium chloride. At the time of mixing, the hydroxylamine solution B (5 ml) was added to the ketone solution. Portions (2 ml) of the reaction mixture were withdrawn periodically and the hydroxylamine was estimated by tritration with thiosulphate.

The data obtained were substituted into the second-order rate equation for unequal concentration of the reactants. In the case of studies on the dependence of reaction rate on ketone concentration, the first-order rate constant (k_1) was calculated from the first-order rate equation.

For pH 7 solution (used in the titration), a buffer containing equal volumes of 0.0570M-disodium hydrogenphosphate and 0.02857M-sodium dihydrogenphosphate was used.

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