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KINETICS OF THE REACTION OF SEMICARBAZIDE WITH SOME TETRAHYDROPYRAN-4-ONES

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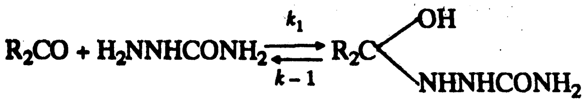
The rates of the reaction of semicarbazide with some substituted tetrahydropyran-4-ones have been measured at 40°, 45° and 50° in 80% ethanol-water (v/v) at pH = 6.4. A large rate retardation is observed as the steric crowding about the carbonyl group increases indicating a rate limiting attack of the base on the carbonyl. The results throw light on the conformations of these compounds.

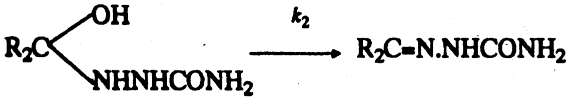
INTRODUCTION

The reaction of semicarbazide with carbonyl compounds is known to proceed through two consecutive steps[1–4]: (i) a general acid catalysed attack of the semicarbazide and (ii) the acid catalysed dehydration of the carbinolamine(I).



$$R_2CO + H_2NNHCONH_2 \underset{k-1}{\overset{k_1}{\rightleftharpoons}} R_2C\begin{cases}OH\\ NHNHCONH_2\end{cases}$$

(i)



$$R_2C\begin{cases}OH\\ NHNHCONH_2\end{cases} \xrightarrow{k_2} R_2C{=}N.NHCONH_2$$

(ii)

Since the attack of the semicarbazide brings about a change in the coordination number of the carbonyl carbon from 3 to 4, the rate data should provide information regarding the steric environment of the carbonyl group. In the present paper we report the kinetic data on the semicarbazone formation of some substituted tetrahydropyran-4-ones to add further evidence to the steric effect.

EXPERIMENTAL

Materials and Methods

The ketones were prepared as previously reported[5]. They were recrystallised to constant m.pt. and dried in vacuo before use. Semicarbazide hydrochloride was purified by the method of Price and Hâmmett[6]. A mixture of acetic acid (0.25 M; 100 ml) and sodium acetate (0.25 M; 100 ml) was made upto one litre with purified ethanol. This was used as solvent for all the runs. The pH of the above solution was found to be 6.4 ± 0.05. All other reagents were of AR grade. The titrimetric procedure of Conant and Bartlett[7] was followed.

RESULTS AND DISCUSSION

The rate constants for the reaction of semicarbazide with ketones are given in Table 1. The second order rate constant for 3-methyl-2,6-diphenyltetrahydropyran-4-one at 30° is calculated using Arrhenius equation for comparison with 2,6-diphenyltetrahydropyran-4-one[8]. As the pilot study was very slow, the kinetics was carried out at higher temperatures.

TABLE 1
SECOND ORDER RATE CONSTANTS FOR THE REACTION OF SEMICARBAZIDE WITH TETRAHYDROPYRAN-4-ONES

Solvent: Ethanol (80% v/v); pH = 6.4

Compound	$k_2 \times 10^2$ litre mol^{-1} s^{-1}				E_a kcal mol^{-1}	$\Delta S^{\neq}$ e.u.
	30°	40°	45°	50°		
1. *Cis*-2,6-diphenyltetrahydropyran-4-one	57.8	—	—	—	—	—
2. 3-Methyl-2, 6-diphenylterahydropyran-4-one	2.03	4.26.	6.06	8.53	14.4	−22.04
3. 3-Ethyl-2, 6-diphenyltetrahydropyran-4-one	—	1.06	1.48	2.08	13.56	−26.20
4. 3, 5-Dimethyl-2,6-diphenyltetrahydropyran-4-one	—	—	—	0.962	—	—

The observed second order rate constants for the reaction of semicarbazide with the ketones (Table 1) clearly indicate the influence of steric factor. The introduction of a methyl group in the 3-position (α to the carbonyl group) lowers the rate by about 30 times. This large steric effect suggests that the step (i) is rate limiting. If the dehydration step were rate limiting, steric acceleration would have been observed.

The rate retardation clearly indicates that the methyl group is equatorially oriented since an adjacent equatorial methyl group will enter into gauche interaction with both the –OH and $-NHNHCONH_2$ groups (Figure 1).

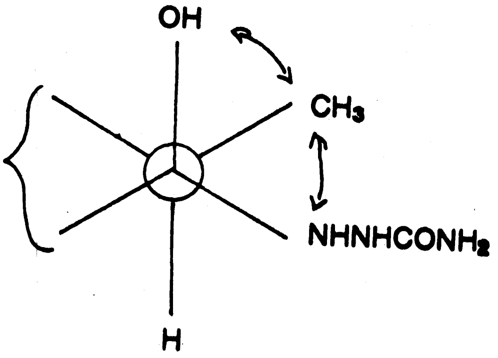


Fig. 1

Same behaviour was observed in the case of similarly substituted piperidin-4-one[8], tetrahydrothiopyran-4-one[9] and cyclohexanone[10]. The relevant rate constants are given in Table 2.

TABLE 2
SECOND ORDER RATE CONSTANTS FOR THE SEMICARBAZONE FORMATION AT 30°

		Compound	$k_2 \times 10^2$ litre mol^{-1} s^{-1}
1.	(a)	2,6-Diphenylpiperidin-4-one	44.6
	(b)	3-Methyl-2,6-diphenylpiperidin-4one	2.30
2.	(a)	*cis*-2,6-Diphenyltetrahydrothiopyran-4-one	42.5
	(b)	3-Methyl-2,6-diphenyltetrahydrothiopyran-4-one	1.03
3.	(a)	Cyclohexanone	40.8
	(b)	2-Methylcyclohexanone	2.79

The rate constant for 3-ethyl-2,6-diphenyltetrahydropyran-4-one is lower than that of the corresponding 3-methyl ketone. With an ethyl group in the 3-position conformations 2(a) and 2(b) are energetically favourable.

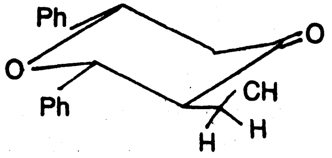


Fig. 2(a)

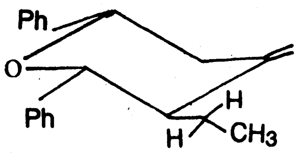


Fig. 2(b)

The lower rate observed provides information regarding the steric environment of the carbonyl group and also establishes the fact that the first step is the rate determining one.

3,5-Dimethyl-2,6-diphenyltetrahydropyran-4-on which has two equatorial methyl groups adjacent to the carbonyl group is extremely slow in the formation of semicarbazone. The reaction could be followed only up to 40%, that too at 50°. Such a striking retardation indicates that there should be a greater steric crowding in the transition state than in the ground state, which is possible only if the step (i) is the rate limiting. If the second step had been rate limiting, a steric enhancement should have been observed as in the case of the dissociation of cyanohydrins of tetrahydropyran-4-ones[11].

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