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Steric and Electronic Effects on the Dehydration Step in Cyclohexanone and Bicyclic Ketones Oxime Formation

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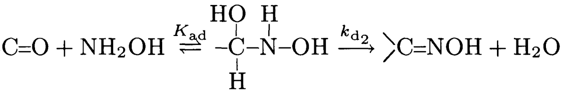
Between pH 4 and pH 13, oxime formation from hydroxylamine with cyclohexanone and bicyclic ketones proceeds with rate limiting dehydration of the addition intermediate which is in equilibrium with the ketone and hydroxylamine. The dehydration step exhibits catalysis by oxonium ion (pH 4 to ca. 8), a pH independent pathway (pH 8 to ca. 10) and catalysis by hydroxide ion (pH ca. 10 to 13). The steric and electronic effects give important insights into the structure of the transition state of the mechanisms of oxonium ion, hydroxide ion catalyzed and spontaneous reaction.

The kinetics, mechanism and catalysis of the reactions of carbonyl compounds with nitrogen nucleophiles have been extensively studied.[1—3] It has been shown that these reactions occur in a two-step process, the first step being attack of the nucleophile on the carbonyl compound and the second step dehydration of the addition intermediate, which is in rapid equilibrium with the reagents. Compared with the wealth of information about the reactions involving aromatic aldehydes and ketones, rather little work has been undertaken on steric and electronic effects on the mechanism of the attack and dehydration step of these reactions.[4—6] Bicyclic systems are attractive for this purpose because of their fixed geometries and because their conformations have been well elucidated.[7] We have discussed the steric and electronic effects on the attack step to form the dihydroxy addition-intermediate in the reaction of hydroxylamine and bicyclic ketones.[8] In this paper, our attention is focused on structural and electronic effects on the dehydration of the dihydroxy addition-intermediate leading to the oxime, in order to obtain criteria for the mechanism of catalysis and the structure of the transition states.

Results and Discussion

Equation 1 indicates the mechanism of oxime formation from carbonyl compounds



$$\rangle\mathrm{C{=}O} + \mathrm{NH_2OH} \overset{K_\mathrm{ad}}{\rightleftharpoons} \text{-}\overset{\mathrm{HO}}{\underset{\mathrm{H}}{\mathrm{C}}}\text{-}\overset{\mathrm{H}}{\mathrm{N}}\text{-}\mathrm{OH} \xrightarrow{k_{\mathrm{d}_2}} \rangle\mathrm{C{=}NOH} + \mathrm{H_2O} \quad (1)$$

At pH values near or below neutrality, most reactions of this type undergo a change in rate-determining step with increasing pH from formation of the addition-intermediate to its dehydration to the products.

The study of structural and electronic effects on the rate of dehydration of the addition intermediate requires reliable determination of K_ad (equilibrium constant of dihydroxy addition-intermediate formation), which is not always possible. The equilibrium constant between hydroxylamine and cyclohexanone was determined in this work and those for the bicyclo ketones were previously determined.[8]

The profiles of log k_{d_2} (k_{d_2}=true second order rate constant) as a function of pH, in the pH range where dehydration of the addition intermediate is the rate-determining step, are indicated for all the ketones studied in Fig. 1.

The ketone with hydroxylamine give an addition intermediate by an equilibrium reaction. Thus, indicating

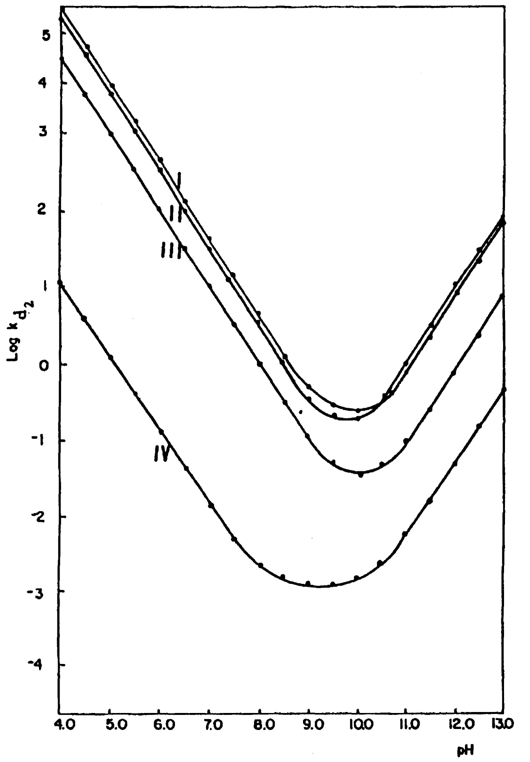


Fig. 1. pH dependence of the logarithms of second-order rate constants k_{d_2} for the dehydration step of oxime formation from bicyclo[2.2.2]octan-2-one (I), cyclohexanone (II), bicyclo[2.2.1]heptan-2-one (III), and 3-chlorobicyclo[2.2.1]heptan-2-one (IV) in 20% ethanol at 25 °C and ionic strength 0.5 M (KCl).

the free ketone concentration as a function of the total concentration of ketone:[3)]

$$[\mathrm{C{=}O}]_f = [\mathrm{C{=}O}]_t K_{ad}/(1 + K_{ad}[\mathrm{NH_2OH}]),$$

the kinetic expression for the oxime formation is:

$$\text{rate} = (k_H[\mathrm{H^+}] + k_o + k_{OH}[\mathrm{OH^-}])[\mathrm{C{=}O}]_t[\mathrm{NH_2OH}]K_{ad}/(1 + K_{ad}[\mathrm{NH_2OH}]), \quad (2)$$

as $k_{obs}=\text{rate}/[\mathrm{C{=}O}]_t$

$$k_{d_2} = k_{obs}/\frac{[\mathrm{NH_2OH}]K_{ad}}{1 + K_{ad}[\mathrm{NH_2OH}]} = k_H[\mathrm{H^+}] + k_o + k_{OH}[\mathrm{OH^-}], \quad (3)$$

equations (2) and (3) are consistent with the experimental results including terms for acid (k_H) and base (k_{OH}) catalysis and a pH independent pathway (k_o).

The curves in Fig. 1 were calculated using Eq. 3, the values of k_H, k_o, and k_{OH} given in Table 1 and the values of K_{ad} reported in the experimental section.

Mechanism of Acid Catalysis. Jencks et al., in studies of the dehydration of the addition intermediate formed from formaldehyde and thiosemicarbazide,[9)] benzaldehyde and semicarbazide,[10)] *p*-chlorobenzaldehyde, and hydrazine[10)] and Cocivera et al., in a study of acetaldehyde and hydroxylamine[11)] demonstrated that these reactions exhibit experimental general acid catalysis with high α Brønsted coefficient (0.83, 0.81, 0.80, and 0.90 respectively). Based on these high values of the α Brønsted coefficient, Lamaty et al.[4)] consider difficult the determination of general acid catalysis, for the dehydration step of oxime formation from some monocyclic, bicyclic, and tricyclic aliphatic ketones, taking into account the probable similar marked catalysis by the solvated proton that makes undetectable the catalysis by other acids.

In the pH range (4 to 8) where the oxonium ion catalyzed dehydration of the addition intermediate is rate-determining it was possible to detect general acid catalysis by different buffers only in the reaction of 3-chlorobicyclo[2.2.1]heptan-2-one. The catalytic rate constants follow the Brønsted relationship and give a value of $\alpha=0.60$ ($r=0.981$).

The solvent deuterium isotope effect for oxonium ion catalysis of the dehydration of bicyclo [2.2.1]heptan-2-one was determined as $k_H/k_D=1.5$. This normal isotope effect is expected for the case of a mechanism of general acid catalysis,[12)] as was observed in the case of formaldehyde thiosemicarbazone formation,[9)] and is a piece of evidence in favor of a mechansim involving general acid catalysis by oxonium ion for the dehydration step of oxime formation for all the ketones studied in this work.

It is important to analyze the amount of C–O bond cleavage in the transition state of the dehydration step considering that there are discrepancies between the parameters that measure it. Studies of secondary α-deuterium isotope effect suggests an early transition state for the reaction of formaldehyde thiosemicarbazone formation.[9)] The same conclusions have been reported for the proton-catalyzed dehydration step of benzaldehyde semicarbazone and phenylhydrazone formation.[13,14)] An early transition state was also indicated for the acid-catalyzed dehydration step of the formation of a series of benzaldehyde hydrazones.[15)]

Lamaty et al.[4)] by comparison of the ratios of the rate of decompostion of cyanohydrins and of hydrogensulfite addition product of cyclohexanone relative to cyclopentanone and cycloheptanone (C_6/C_5 and C_6/C_7), with the ratios of the rates of dehydration of the addition intermediate of hydroxylamine of the same ketones, proposed that in the transition state of the oxonium ion catalyzed dehydration the carbon atom reaction center has a configuration near to sp^3.

However, the ρ value of -1.9 for acid catalysis of the dehydration step of benzaldehyde semicarbazone formation, which is 90% of the value for product formation according to Funderburk and Jencks[10)] suggest a large amount of C–O bond cleavage in the transition state.

In this case it should be noted that the rate of oxonium catalyzed dehydration in forming the oxime of 3-chloro[2.2.1]heptan-2-one is 746 and 3346 times slower than those for bicyclo[2.2.1]heptan-2-one and bicyclo [2.2.2]octan-2-one (See Table 2) indicating a notable instability of the transition state caused by the electron-withdrawing effect of the chlorine atom.

The pK_as of the addition intermediates, protonated on the hydroxyl group bonded to the carbon atom, corresponding to bicyclo[2.2.1]heptan-2-one and 3-chlorobicyclo[2.2.1]heptan-2-one were calculated as -3.29 and -5.39 respectively (see experimental part). The addition intermediate of hydroxylamine on bicyclo[2.2.1]-heptan-2-one is 126 times more basic than that of 3-chlorobicyclo[2.2.1]heptan-2-one. This difference should be attributed fundamentally to the destabilizing effect of the electron-withdrawing chlorine atom on the complete positive charge of the protonated oxygen atom of the addition intermediate. However, the effect of the chlorine atom is larger on the oxonium ion catalyzed rate constant of the dehydration step of the addition intermediate corresponding to 3-chlorobicyclo[2.2.1]heptan-2-one that is 746 slower than that of the corresponding bicyclo[2.2.1]heptan-2-one.

If the cleavage of the C–O bond is very early the structure of the transition state should be similar to that of the protonated intermediate. But, it is not the case as is indicated by the chlorine atom effect that decreases the rate constant of the oxonium ion catalyzed dehydration more than it decreases the basicity of the additon intermediate. This fact suggest that should exist a moderate cleavage of the C–O bond in the transition state that leaves the central carbon atom with some positive charge but, probably, with a configuration nearer to sp^3 than sp^2 because, it is clear that, do not exist delocalization of the electron density of the nitrogen atom as

Table 1. Oxonium and Hydroxide Catalyzed Rate Constants and Spontaneous Rate Constants for α-Aminoalcohol Dehydration Step for Oxime Formation from Ketones and Cyclohexanone[a,b)]

Ketones	$k_H(M^{-2}\ min^{-1})$	$k_{OH}(M^{-2}\ min^{-1})$	$k_o(M^{-1}\ min^{-1})$
Cyclohexanone	2.7×10^8	689	4.31×10^{-2}
Bicyclo[2.2.1]heptan-2-one	9.48×10^7	69	2.05×10^{-2}
Bicyclo[2.2.2]octan-2-one	4.25×10^8	667	1.15×10^{-1}
3-Chlorobicyclo-[2.2.1]heptan-2-one	1.27×10^5	4.54	9.82×10^{-4}

a) 20% ethanol, 25 °C, μ=0.5 (KCl). b) In most cases the data agree within 3%.

Table 2. Rate Constants Ratio for the Reactions between Bicyclic Ketones and Hydroxylamine[a)]

	k_H	k_o	k_{OH}
BO/BH	4.48	5.61	9.66
BO/ClBH	3346	117	147
BH/ClBH	746	21	15

d) BO=bicyclo[2.2.2]octan-2-one; BH=bicyclo[2.2.1]-heptan-2-one; ClBH=3-chlorobicyclo[2.2.1]heptan-2-one.

can be seen in the pH independent region.

This transition state with a moderate cleavage of the C–O bond but with the carbon atom nearer to sp^3 than sp^2 conciliate the results of the secondary α-deuterium isotope effect[9,13,14)] that suggest little change from the sp^3 hybridization of the reactants and the others parameters that suggest some advanced C–O cleavage.[10)]

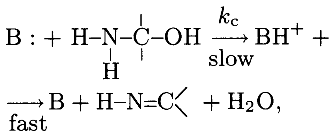
It is interesting to note that the pK_a of the protonated addition intermediate corresponding to the unsubstituted bicyclic ketones indicate that the proton transfer from them to water usually will be not diffusion controlled[16)] (the ΔpK_a between the protonated addition intermediates and water is less than 2 units) and for this will exist as relatively stable species under the conditions of the experiments. Thus, it is possible to conclude that in these cases, similarly to the case of the reaction between formaldehyde and thiosemicarbazide,[9)] general-acid catalysis can occur even when it is not required to occur by the nonexistence of the intermediate for a stepwise reaction because the concerted catalysis provides a low-energy path for the reaction.

pH-Independent Reaction. In this process, with the poor leaving hydroxide group, it is reasonable to assume a transition state with more extensive C–O cleavage and with the carbon atom nearer to sp^2 than sp^3. The ratio between the rate constants of bicyclo[2.2.1]-heptan-2-one and 3-chlorobicyclo[2.2.1]heptan-2-one in the pH independent region is 21, that compared with the same ratio in the acid-catalyzed region (746), indicates that the positive charge on the central carbon atom is much less significant in this region. The delocalization of the electrons from the nitrogen atom to the sp^2 carbon atom giving some double bond character to the C–N bond explain this fact.

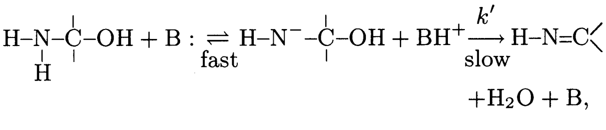
The value of the ratio between the spontaneous rate constants of bicyclo[2.2.2]octan-2-one and bicyclo[2.2.1]-heptan-2-one that is bigger than the same ratio of the oxonium ion catalytic rate constants (Table 2) leads to the same conclusion considering the high angular strain for double bond formation in the last ketone.

Mechanism of Base Catalysis. The hydroxide ion catalyzed mechanism of dehydration of the addition intermediate from carbonyl compounds and nitrogen bases has been the object of controversy. In benzaldehyde oxime formation an inverse relation k_{OH}/k_{OD}= 0.71 was indicated by Williams and Bender[17)] as support of specific-base catalyzed mechanism. However, Jencks[1)] is of the opinion that it is not possible, on the basis of this result alone, to define the mechansim of this reaction due to theoretical and experimental uncertainties.

Jencks et al.[18)] observed that the dehydration of the addition intermediate derived from p-chlorobenzaldehyde and thiosemicarbazide exhibits general-base catalysis with β=0.71. In the reactions studied in this work, it was not possible to demonstrate clearly experimental general-base catalysis. Thus, the two possible mechanisms for hydroxide ion are indicated in Eqs. 4 and 5.



$$B: + H\text{-}\underset{H}{N}\text{-}C\text{-}OH \xrightarrow[\text{slow}]{k_c} BH^+ + H\text{-}N{=}C\langle\ + OH^- \xrightarrow[\text{fast}]{} B + H\text{-}N{=}C\langle\ + H_2O, \qquad (4)$$



$$H\text{-}\underset{H}{N}\text{-}C\text{-}OH + B: \underset{\text{fast}}{\rightleftharpoons} H\text{-}N^-\text{-}C\text{-}OH + BH^+ \xrightarrow[\text{slow}]{k'} H\text{-}N{=}C\langle\ + H_2O + B, \qquad (5)$$

where k' of Eq. 5 is $=k_cK_w/K_a$ (K_w=dissociation constant of water, K_a=dissociation constant of α-aminoalcohol as acid).

The pK_a for the ionization of the N–H bond of the addition intermediate can be calculated from the pK_a of ionization of ammonia, which is 35.[19)] Considering that the pK_a of the ammonium ion is $\simeq$9, that the pK_a of NH_3OH is $\simeq$6, and that the pK_a for anion formation from ammonia is 1.3 times as sensitive to electron withdrawal substituents as the pK_a for removal of a proton from the corresponding ammonium ion,[18] we obtain $35-(9-6)\times1.3=31$. Since the hydroxymethyl group has been shown to lower the pK of protonated amines by 2—3 units,[18] the pK_a for ionization of the N–H bond of the addition intermediate derived from the unsubstituted bicyclo ketones and hydroxylamine is approximately 28. Thus, the value of k' for the bicyclo[2.2.1]heptan-2-one, that exhibits the smallest rate constant, would be 6.9×10^{15} M^{-1} min^{-1}, i.e. much greater than the limiting value for a diffusion-controlled reaction (1 M=1 mol dm^{-3}).[19] Based on this line of reasoning, the mechanism of specific base general acid catalysis (Eq. 5) can be ruled out.

An analysis of the structural effects on the rate constants also gives some insights into the structure of the transition state of this mechanism. The ratio of the hydroxide ion catalytic rate constants betwen bicyclo[2.2.2]octan-2-one and bicyclo[2.2.1]heptan-2-one and between bicyclo[2.2.2]octan-2-one and 3-chlorobicyclo[2.2.1]heptan-2-one are 9.66 and 147 respectively. The same ratios for the spontaneous rate constants are 5.61 and 117, respectively. This fact suggests that the $>$C=N formation is more significant in the transition state of the hydroxide ion catalyzed region. The ratio differences, between the two regions of pH, indicating the lower angular strain upon double bond formation, going from the addition intermediate to the oxime, in case of bicyclo[2.2.2]octan-2-one.

Considering the Brønsted coefficient ($\beta=0.42$) determined for the general base catalysis, exhibiting the dehydration step of the reaction between 3-quinuclidinone and hydroxylamine[20] and having a similar profile of log k_2 vs. pH of the dehydration step of the other bicyclic ketones, we may assume that the general-base catalyzed dehydration for oxime formation from these ketones should have a transition state with a moderately developed bond between the proton being abstracted and the base, with the leaving group weakly bonded to the central carbon atom and with significant development of the carbon-nitrogen double bond. In this case the driving force of the reaction could be the delocalization of the electron pair of the nitrogen atom to form the C–N double bond.

Experimental

Materials: Organic reagents employed were comercially available products and were either redistilled or recrystallyzed. Hydroxylamine hydrochloride was purified by recrystallization from ethanol-water and the solutions were prepared just prior to use. Inorganic chemicals and carboxylic acids used in buffers were reagent grade and were used without further purification.

Kenetics: The method has been described in a previous paper.[8] Second-order rate constants (k_{d_2}) were calculated from Eq. 3. Third-order rate constants (k_H and k_{OH}) were obtained from the slopes of plots of second-order rate constants (k_{d_2}) against the concentration of oxonium and hydroxide ion respectively. k_o was drawn directly from the profile of log k_{d_2} vs. pH.

Equilibrium Constant Determination: The equilibrium constant, K_{ad} for the addition intermediate formation from hydroxylamine and cyclohexanone was determined spectrophotometrically, from the initial decrease in absorbance at 285 nm extrapolated to zero time upon addition of approximately 1.67×10^{-2} M cyclohexanone to 0.2—0.5 M hydroxylamine solutions, in 0.01 M borate buffer, pH=9.6, 20% aqueous ethanol and ionic strength 0.5 M (KCl). The value obtained is the average of 15 determinations. The calculated values of the fraction of ketone converted to addition intermediate were based on an assumed absorbance of zero for the addition compound at 285 nm. K_{ad} for cyclohexanone is 8.15 ± 0.15. The other bicyclic ketones were determined previously[8]: for bicyclo[2.2.1]heptan-2-one 0.58 ± 0.07; for bicyclo[2.2.2]octan-2-one 0.12 ±0.03; for 3-chlorobicyclo[2.2.1]heptan-2-one $2.17\pm$ 0.06.

Isotopic Effect: The kinetics were determined in water and in deuterium oxide solutions at ionic strength 0.5 M (KCl). Values of pD (6.9) were obtained from the measured pH values using the relation pD=pH+0.4. The final deuterium oxide content was greater than 97% in all cases. The value obtained $k_H/k_D=1.50\pm0.05$ is the average of three determinations.

pK_a Calculation: Based on analogy it is possible to consider that the pK_a of 2-hydroxybicyclo[2.2.2]octan-2-one as a base should be similar to that of ethanol, pK_a= -1.94.[21] Considering that the behavior of the basicity of alcohols is similar to that of amines, it is possible to calculate the base-weakening effect of the –NHOH group using the equation $-\Delta pK_a=0.28+0.87\ \sigma^*$.[22] As the σ^* of –NHOH is 0.30[22], the calculated ΔpK_a is -0.54. This value corresponds to the substituent attached to β-carbon, but as in this case it is attached to α-carbon, assuming a normal behavior of it in this position, the ΔpK_a will be $-0.54/0.40=-1.35$. Consequently, the pK_a of the addition intermediate of bicyclo[2.2.2]octan-2-one, protonated on the hydroxyl group bonded to the carbon atom, should be $-1.94-1.35=-3.29$. The protonated addition intermediate of bicyclo[2.2.1]heptan-2-one should have approximately the same pK_a, but in the case of the addition intermediate of 3-chlorobicyclo [2.2.1]heptan-2-one, the base weakening effect of the chlorine atom on β-carbon must be considered. From values given in the literature this effect is $\Delta pK_a=-2.1$.[22] Thus the pK_a of the protonated addition intermediate of 3-chlorobicyclo[2.2.1]heptan-2-one is -5.39.

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