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ADDITION OF HYDROXYLAMINE TO CYCLOHEXANONE AND BICYCLIC KETONES. STERIC, ELECTRONIC AND HYDROGEN BONDING EFFECTS ON THE GENERAL MECHANISM OF ADDITION OF AMINES TO CARBONYL COMPOUNDS

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Three different types of pH–rate profiles were observed for the addition of amines to carbonyl compounds, depending on the relative predominance, at weakly acidic pH, of either a concerted or a stepwise mechanism. The predominant mechanism depends on the basicity of the amine and the mutual equilibrium affinity for adduct formation between the carbonyl compound and the amine. The reaction of hydroxylamine with cyclohexanone and bicyclic ketones was studied in order to examine the roles of steric and electronic effects in this mechanism. Cyclohexanone and 3-chlorobicyclo[2.2.1]heptan-2-one exhibit the profile expected for a single change in the rate-determining step with increasing pH from uncatalysed attack of the amine on the carbonyl group to hydronium ion-catalysed dehydration of the carbinolamine. In contrast, both bicyclo [2.2.1]heptan-2-one and bicyclo[2.2.2]octan-2-one show an unexpected profile with two negative breaks and five kinetically significant regions. This profile is explained by stabilization of the zwitterionic intermediate $T^{\pm}$ by intramolecular hydrogen bonding, leading to the formation of the carbinolamine by a stepwise mechanism at weakly acidic pH.

INTRODUCTION

The kinetics, mechanism and catalysis of the addition of amines to carbonyl compounds have been widely studied.[1] However, compared with the vast amount of information for reactions involving aromatic aldehydes and ketones, little work has been undertaken on steric and electronic effects on the mechanism of addition of amines to alicyclic aldehydes and ketones.[2] Bicyclic systems have been used as substrates particularly for the examination of steric requirements of organic reactions.[3] These compounds are attractive for this purpose because of their known geometries and fixed conformations.[4] In this paper, we discuss the steric and electronic effects on the formation of carbinolamines from hydroxylamine and bicyclic ketones in relation to the general mechanism of addition of amines to the carbonyl group suggested by Sayer *et al.*[5]

RESULTS AND DISCUSSION

Two mechanisms have been demonstrated to exist for general acid catalysis of carbinolamine formation (Scheme 1):[6] a concerted mechanism (I), i.e. a process in which carbon—nitrogen bond formation and protonation of the oxygen atom of the carbonyl group are in some sense 'concerted'; and a stepwise mechanism (II) involving initial formation of an unstable zwitterionic form ($T^{\pm}$) of the carbinolamine which is subsequently trapped by proton transfer from an acid or by an intermolecular proton switch that converts $T^{\pm}$ to T^{0}.

Sayer *et al.*,[5] considering these mechanisms, suggested that in aqueous solution under acidic or neutral conditions, it is possible to predict, based in the stability of the zwitterionic intermediate $T^{\pm}$, that (i) for very weakly basic amines or carbonyl compounds for which

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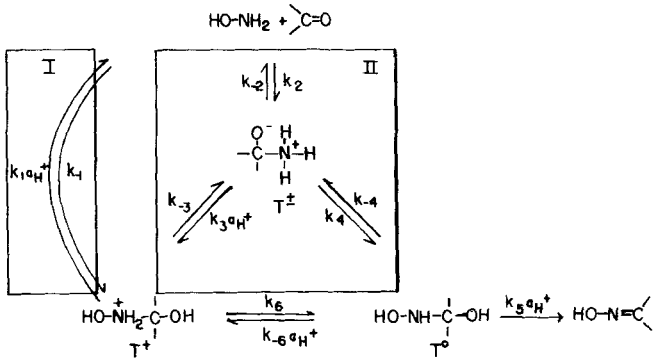


Scheme 1

the equilibrium constant for carbinolamine formation (K_{ad}) is small the zwitterionic intermediate will be very unstable and the reaction will proceed by the concerted pathway (I); (ii) for amines of moderate basicity and carbonyl compounds of reasonable equilibrium affinity for amine addition, the zwitterionic intermediate will be relatively stable and the stepwise pathway (II) is favoured.

The shape of the observed pH–rate profiles for this reaction depends on the relative magnitudes of the concerted and stepwise mechanisms. Sayer *et al.*[5] pointed out that three kinds of pH–rate profiles are observed according to the magnitudes of the two mechanisms mentioned. A pH–rate profile of type A, with one negative break and three regions that correspond to three significant rate constants, is observed with weakly basic amines and small K_{ad}. In this case the stepwise pathway (II) for hydronium ion catalysis is unfavourable relative to the concerted process, which is the only significant route for the addition step. The pH-independent region reflects a stepwise mechanism involving rate-determining solvent-mediated isomerization of $T^{\pm}$ to T^{0}. The pH–rate profile of type B, with two negative breaks and five regions that correspond to five significant rate constants, is observed with amines of moderate basicity and equilibrium affinity for the carbonyl group. In this case, hydronium ion catalysis, via the stepwise mechanism (II), is significant relative to the concerted pathway (I). Finally, the pH–rate profile of type C, with one negative break at low pH and three regions, is observed with amines of stronger basicity and high equilibrium affinity. In this case, the rate of the stepwise pathway is increased and exceeds the rate of the hydronium ion-catalysed dehydration step and the only change in the rate-determining step observed is the transition from uncatalysed attack (k_2) to hydronium ion-catalysed dehydration ($K_{ad}k_5$) on increasing the pH.

In Figure 1, the plot of log k_2 (k_2 = second-order rate constant) as a function of pH is shown for the reactions of hydroxylamine with acetone, cyclohexanone, bicyclo[2.2.1]heptan-2-one, bicyclo[2.2.2]octan-2-one and 3-chlorobicyclo[2.2.1]heptan-2-one.

Acetone, cyclohexanone and 3-chlorobicyclo[2.2.1]heptan-2-one show a *profile of type C*, as would be expected considering the basicity of hydroxylamine and the equilibrium constant K_{ad} for carbinolamine formation.

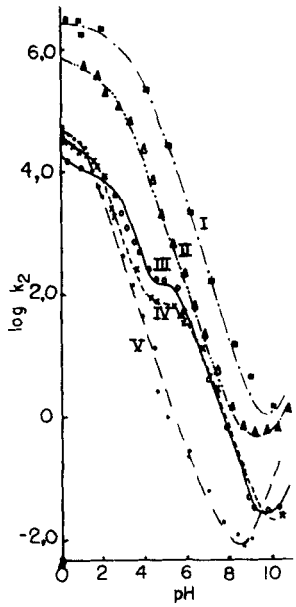


Figure 1. pH dependence of the logarithms of second-order rate constants for oxime formation from cyclohexanone (■) (I), acetone (△) (II), bicyclo[2.2.2]octan-2-one (○) (III), bicyclo[2.2.1]heptan-2-one (×) (IV) and 3-chlorobicyclo[2.2.1]heptan-2-one (•) (V) in 20% ethanol at 25 °C and ionic strength 0·5, except acetone (water, 25 °C, μ = 0·2–0·32). (From Refs 14 and 31)

Surprisingly, bicylo[2.2.2]octan-2-one and bicyclo[2.2.1]heptan-2-one show a profile of type B with two negative breaks and five regions, corresponding to (i) at very low pH (<1), concerted general acid-catalysed attack of hydroxylamine on the carbonyl compound (k_1); (ii) between pH 1 and 2·5, uncatalysed attack (k_2); (iii) between pH 2·5 and 4, a proton transfer process that will be discussed below; (iv) between pH 4 and 6, solvent-catalysed proton transfer from $T^{\pm}$ to T^0 ($K_n k_4$; $K_n = k_2/k_{-2}$); and (v) at pH > 6, hydronium ion-catalysed dehydration of the carbinolamine ($K_{ad}k_5$). This profile was unexpected for a nucleophile such as hydroxylamine and the magnitudes of K_{ad} for carbinolamine formation of these ketones.

Steady-state treatment of the mechanism in Scheme 1 yields equations (1) and (2) for product formation in the regions of rate-determining carbinolamine formation and dehydration, respectively.

$$k_{ad} = k_{aH} + k_2(K_n k_4 + K_n k_3)/k_2 + K_n k_4 + K_n k_4 + K_n k_{3aH} \quad (1)$$

$$k_{deh} = k_{ad}K_{ad}k_{5aH}/k_{ad} + K_{ad}k_{5aH} \quad (2)$$

The solid curves in Figure 1 were calculated employing equations (1) and (2) together with the rate constants in Table 1. The fit between the experimental data and the theoretical curve is acceptable.

In order to interpret the steric and electronic effects for the ketones, we shall discuss the equilibrium for carbinolamine formation and the different steps of the reaction, especially the proton-transfer step.

Equilibrium constants for carbinolamine formation

The equilibrium constants for carbinolamine formation between hydroxylamine and the ketones studied are given in Table 2. The observed difference between the K_{ad} values for acetone and bicyclo[2.2.1]heptan-2-one cannot explain the change in the pH–rate profile from type C for acetone to type B for bicyclo[2.2.1]heptan-2-one.

The value of K_{ad} for bicyclo[2.2.1]heptan-2-one is five times greater than that for bicyclo[2.2.2]octan-2-one. There are a number of steric factors which might contribute to these observed equilibrium constants. Steric factors[7,8] include angle strain, non-bonded repulsion and eclipsing or torsional strain. These factors should be considered on going from the ketone to the carbinolamine. In bicyclo[2.2.1]heptan-2-one, the carbonyl angle is 107°,[9] whereas the $C_1-C_2-C_3$ angle in the carbinolamine is 104·3°. In contrast, the angle of the carbonyl group in bicyclo[2.2.2]octan-2-one is 116°,[10] and normal for the addition product.[3d] Hence the decrease in the angle strain of the carbonyl group relative to the carbinolamine is greater for bicyclo[2.2.1]heptan-2-one (8°) than for bicyclo[2.2.2]octan-2-one (4°) and should result in a greater gain in energy in the first case. The energy of non-bonded interactions[7,11] and torsional strain,[7,12] which should be greater for the addition equilibrium of bicyclo[2.2.1]heptan-2-one, would not be expected to compensate the favourable reduction in angle strain of the carbonyl group.

The same factors explain the differences between the

Table 1. Kinetic constants for carbinolamine formation from hydroxylamine and ketones at 25 °C[a]

Compound	k_1 ($l^2 mol^{-2} s^{-1}$)	k_2 ($l mol^{-2} s^{-1}$)	$K_n k_3$ ($l^2 mol^{-2} s^{-1}$)	$K_n k_4$ ($l mol^{-2} s^{-1}$)
Cyclohexanone		$2·5 \times 10^6$		
Bicyclo[2.2.1]heptan-2-one	$4·0 \times 10^4$	$2·0 \times 10^4$	$6·7 \times 10^5$	68
Bicyclo[2.2.2]octan-2-one	$2·0 \times 10^4$	$1·0 \times 10^4$	$3·2 \times 10^6$	148
3-Chlorobicyclo[2.2.1]heptan-2-one	$4·7 \times 10^4$	$2·7 \times 10^4$		

[a]Ionic strength 0·5 (KCl) and 20% ethanol.

Table 2. Equilibrium constants, K_{ad}, for carbinolamine formation from ketones and hydroxylamine at 25 °C

Ketone	NH_2OH (M)	Solvent	μ	pH	K_{ad} ($l mol^{-1}$)	Ref.
Cyclohexanone	0·067–0·67	Water	3·2	7·6	6·5	14
Acetone	0·4–3·2	Water	3·2	7·7	1·0	14
Bicyclo[2.2.1]heptanone	0·29–2·5	20% EtOH	0·5	9·6	0·58	This work
3-Chlorobicyclo[2.2.1]heptanone	0·19–0·58	20% EtOH	0·5	9·6	2·2	This work
Bicyclo[2.2.2]octanone	0·65–2·5	20% EtOH	0·5	9·6	0·12	This work

K_{ad} values of cyclopentanone (0·26) and of cyclkoheptanone (0·093) in 40% methanol.[2] The inductive effect of the chlorine atom, which increases the electrophilicity of the carbonyl group, explains the higher value of K_{ad} for 3-chlorobicyclo[2.2.1]heptan-2-one relative to bicyclo[2.2.1]heptan-2-one.

Cyclohexanone has two of its α-hydrogen atoms almost in the same plane as the carbonyl group, whereas its carbinolamine has all the bonds staggered. Consequently, the change is energically favourable and this explains the fact that cyclohexanone has the largest K_{ad}.

Uncatalysed attack step

As indicated in Table 1, the order of the rate constants for the uncatalysed attack of hydroxylamine on the carbonyl group (k_2) is cyclohexanone > 3-chlorobicyclo[2.2.1]heptan-2-one > bicyclo[2.2.1]heptan-2-one > bicyclo[2.2.2]octan-2-one. In this case, both steric effects on the approach of the hydroxylamine and the strain of the carbonyl group should be considered. Cyclohexanone should exhibit the smallest steric effect on the approach of hydroxylamine because it has no internal bridge. The fact that the rate constant for bicyclo[2.2.1]heptan-2-one is greater than that for bicyclo[2.2.2]octan-2-one is consistent with the smaller steric hindrance of a methylene vs an ethylene bridge on the attack and, secondly, to loss of strain in the carbonyl groups. An increase in the electrophilic nature of the carbonyl group on the introduction of the chlorine atom explains the higher reactivity of 3-chlorobicyclo[2.2.1]heptan-2-one relative to bicyclo[2.2.1]heptan-2-one.

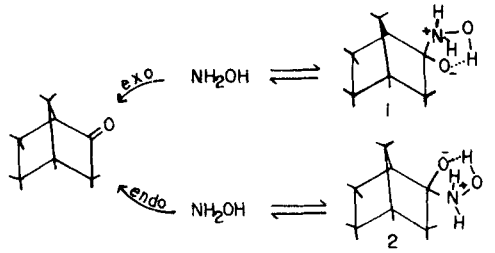
Proton transfer step

In the region of rate-determining proton transfer (between *ca* pH 2 and 4), some surprising facts were observed. First, an increase in solvent viscosity (50% aqueous glycerol) does not significantly affect the catalytic rate constants of the reaction. If the diffusion-controlled process of proton transfer were rate limiting, as might be expected according to Jencks,[1] the catalytic rate constant should exhibit a retardation of a factor of *ca* 6 (from the relationship $k^{H_2O}/k^{glyc} = \eta^{glyc}/\eta^{H_2O} = 6{\cdot}03$)[13] in aqueous glycerol solution without added salt. Second, under the conditions mentioned above, the second-order rate constant is insensitive to the concentration of different carboxylic acid buffers. One would have expected to observe general acid catalysis with a non-linear Brønsted plot.[1] The experimental kinetic solvent isotopic effect in the region of proton transfer is $k_H/k_D = 0{\cdot}85$. Considering the above facts it is clear that a special behaviour of this reaction occurs in this pH region.

It is interesting that the rate constant ($K_{ad}k_5$) for the proton-catalysed dehydration of acetone carbinolamine[14] ($1{\cdot}8 \times 10^6$ l^2 mol^{-2} s^{-1}) to the oxime is very similar to those for bicyclo[2.2.1.]heptan-2-one carbinolamine ($1{\cdot}2 \times 10^6$ l^{2}mol^{-2}s^{-1}) and bicyclo[2.2.2]octan-2-one carbinolamine ($1{\cdot}1 \times 10^6$ l^{2}mol^{-2}s^{-1}), but different to that for cyclohexanone carbinolamine ($16{\cdot}2 \times 10^6$ l^{2}mol^{-2}s^{-1}); however, cyclohexanone and acetone exhibit a profile of type C, whereas the bicyclic ketones exhibit a profile of type B. Since the nucleophile is the same, this fact cannot be explained on the basis of the equilibrium constants for carbinolamine formation, these being similar for acetone and norbornan-2-one. Consequently, a factor that makes the rate constants for the proton-transfer step ($1{\cdot}3 \times 10^4$ l^{2}mol^{-2}s^{-1} for bicyclo[2.2.1]heptan-2-one and $3{\cdot}3 \times 10^4$ l^{2}mol^{-2}s^{-1} for bicyclo[2.2.2]octan-2-one approximately 100 times smaller than those for the dehydration step ($K_{ad}k_5$) would explain the profile of type B.

In the case of 3-chlorobicyclo[2.2.1]heptan-2-one, the profile is of type C. The inductive effect of the chloride atom decreases the rate constant for hydronium-catalysed dehydration ($K_{ad}k_5 = 4{\cdot}6 \times 10^3$ l^{2}mol^{-2}s^{-1}) by a factor of 1000 relative to the other bicyclic ketones, making it much slower than the rate constant for proton transfer.

Hydroxylamine and bicyclo[2.2.1]heptan-2-one can potentially form two tetrahedral intermediates ($T^{\pm}$) according to the direction of attack of hydroxylamine on the carbonyl group, although the *exo* side is preferred owing to steric effects, which have been extensively studied.[15] The analysis of these intermediates using molecular models shows that when the attack is from the *exo* side, the conformation and the steric interactions with hydrogen atoms at C-1, C-7, C-3 and C-4 favour the formation of a hydrogen bond in a five-membered ring between the hydroxyl group of hydroxylamine and the carbonyl oxygen (structure **1**). When the attack is from the *endo* side, the conformation and the steric interactions with the hydrogen atoms of C-5 and C-6, which determine the position of the nitrogen atom, lead to the formation of a hydrogen bond as in the previous case (structure **2**). The same result is expected for the tetrahedral intermediate formed by attack on either side of bicyclo[2.2.2]octan-2-one. The existence and importance, in cyclic systems with a five-membered ring, of hydrogen bonding has been shown.[1,16] It is probable that the conformational effects[8] of electrostatic attraction between the charged groups contribute to the stabilization of the tetrahedral

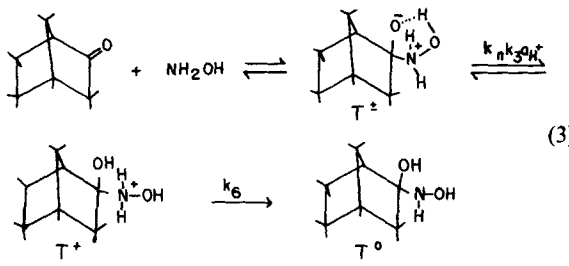


intermediate and, consequently, to stronger hydrogen bond formation.

A similar stabilization by hydrogen bonding for the carbinolamines of semicarbazide, hydrazide and hydroxylamine and for the transition state of the reaction of attack of hydroxylamine on the carbonyl group of acylated compounds was suggested by Jencks.[14,17]

The study of proton transfer reactions by fast reaction techniques has shown that the incorporation of an acidic proton into an internal hydrogen bond can slow its rate of transfer to a base by several orders of magnitude.[18] Similarly, the internal hydrogen bond in the tetrahedral intermediate may well be responsible for the slowness of the proton transfer from the hydronium ion to the negatively charged oxygen.

This fact, and equation (3), indicate that if the proton transfer is not diffusion-controlled, two steps could be rate determining for the reaction, i.e. $K_n k_3$ or k_6.



(3)

If k_6 is rate determining, the lack of a viscosity effect in 50% aqueous glycerol would not be unexpected because proton transfer from T^+ to water should not be diffusion controlled. The kinetic isotope effect of less than unity does not eliminate this mechanism, since this is the direction expected for reactions in which a pre-equilibrium precedes the rate-determining step.[19] Since the pK_a values of hydroxylamine,[20] *N*-methylhydroxylamine[20] and *N*-cyclohexylhydroxylamine[21] are very close (*ca* 6) and taking the base-weakening effect of the hydroxyl group attached to the α-carbon atom (calculated by the ΔpK_a method[22]) to be $-3{\cdot}69$, the pK_a (of the ammonium group) of the intermediate T^+ can be estimated to be 2·39. Hence one might expect to observe general base catalysis by formate and acetate buffers; nonetheless, no such catalysis could be detected using pH 3·15 and 3·75 formate buffers (0·1–0·5 M) and pH 4·15 acetate buffer (0·1–0·5 M).

In addition to k_6, the kinetic isotope effect does not eliminate $K_n k_3$ as rate determining. Primary kinetic solvent isotope effects on proton-transfer reactions have maximum values when the pK_a values of the proton donor and the protonated acceptor are similar.[23] When $\Delta pK_a \ll 1$, values near to or less than unity can be obtained.[23] This would be the case in our system provided that the pK_a of hydronium ion is smaller than that of the basic group of the intermediate ($T^{\pm}$). In addition, an internal hydrogen bond has been suggested to be responsible for the lack of detectable general acid catalysis by carboxylic acids in the formation of the carbinolamine from phenylhydrazine and 2′-hydroxyacetophenone[24] and in the proton-transfer step of the reaction between pyridine 2-carboxaldehyde and phenylhydrazine.[25] The most probable rate-determining step is thus proton transfer from the hydronium ion to the $T^{\pm}$ intermediate ($K_n k_3$).

Considering that the rate of proton transfer should be approximately the same in both cases, the higher rate constant for bicyclo[2.2.2]octan-2-one than bicyclo[2.2.1]heptan-2-one probably indicates that the tetrahedral intermediate is more stabilized in the former case. Thus, the values of the equilibrium constant for tetrahedral zwitterionic intermediate formation (K_n) would be in the inverse order of the values for carbinolamine formation (K_{ad}) for the two bicyclic ketones.

The most important conclusion of this work is that the stability of the tetrahedral intermediate ($T^{\pm}$) formed from alicyclic ketones and amines cannot be predicted only from the basicity of the amine and the equilibrium affinity of the carbonyl compound. Conformational effects (steric and electronic) can introduce new factors that affect the stability of this intermediate, altering the pathway of the mechanism and hence the pH–rate profile of these reactions. Thus, the general mechanism of addition of amines to carbonyl compounds suggested by Sayer *et al.*[5] is still an important guide for the prediction of these mechanisms, but additional factors such as conformational effects should be considered when applied to compounds of the type studied in this work.

EXPERIMENTAL

Materials. Organic reagents were obtained commercially and were either redistilled or recrystallized. Inorganic chemicals and formic and acetic acids used in buffers were of reagent grade and were used without further purification. Solutions of hydroxylamine were prepared just prior to use, as were those of carboxylic acids in 20% aqueous ethanol to avoid esterification.

Kinetics. Reaction of the ketones with hydroxylamine, in 20% v/v aqueous ethanol at 25·0 °C and ionic strength 0·50 (KCl), were followed on a Varian DMS 80 spectrophotometer, equipped with a thermostated cell holder, by monitoring the formation of the oxime at 243 nm for the bicyclic ketones and at 222 nm for cyclohexanone and by monitoring the disappearance of the ketones at 285 nm. The concentrations of the carbonyl compounds were 5×10^{-5} M for cyclohexanone and 2×10^{-3} M for the

bicyclic ketones. A sufficient excess of hydroxylamine was employed to ensure pseudo-first-order kinetic behaviour. The determinations of the rate constants were realized using known procedures.[26] The value of the pK_a of hydroxylamine was taken to be the same as that in water; this procedure has been justified in detail by Bastos and Amaral.[27] The pH measurements for kinetic experiments were realized with a pH meter standardized following Bates's method.[28]

The method of Sayer and Edman[29] was followed to determine rate constants at apparent pH 2·87, 3·13 and 3·43 and the pK_a of hydroxylamine in 50% aqueous glycerol and ionic strength 0·50.

The kinetics were determined in water and in deuterium oxide solutions at ionic strength 0·50. Values of pD (2·4 and 2·8) were obtained from the measured pH values using the relationship[30] pD = pH + 0·40. The final deuterium oxide content was greater than 97% in all cases.

Equilibrium constants. The equilibrium constants K_{ad} for neutral carbinolamine formation from hydroxylamine and bicyclic ketones at pH 9·6 (0·01 M borate buffer), 20% aqueous ethanol and ionic strength 0·5 M (KCl) were determined spectrophotometrically[14] by measuring the ketone absorbance change at 285 nm, extrapolated to time zero, on mixing a solution of bicyclic ketone with five concentrations of hydroxylamine (between 0·2 and 0·5 M). The values obtained are the average of 20 determinations: bicyclo[2.2.1]heptan-2-one, $K_{ad} = 0·54 \pm 0·07$; bicyclo[2.2.2]octan-2-one, $K_{ad} = 0·12 \pm 0·03$; 3-chlorobicyclo[2.2.1]heptan-2-one, $K_{ad} = 2·17 \pm 0·06$. The calculated values of the fraction of ketones converted to carbinolamine were based on an assumed absorbance of zero for the carbinolamine addition compound at 285 nm. This assumption was verified experimentally for the hydrogensulphite addition compound (2–4% of the initial ketone absorbance value remained after addition of 0·1 M sodium hydrogensulphite) and for measurements of the absorbance at high base concentration and extrapolation to infinite base concentration.[14]

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