The "α-Effect" of Hydroxamic Acids

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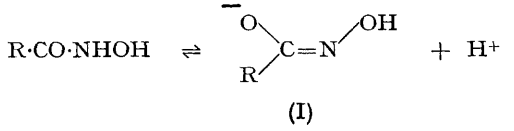
Summary A new mechanism for the acylation of hydroxamic acids, ionised in the oximino form, is suggested involving intramolecular base catalysis; *N*-methylhydroxamic acids are considered to react by a different mechanism.

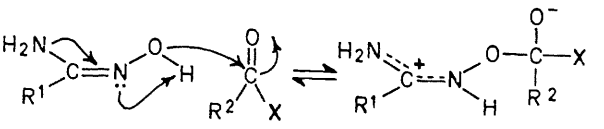
IN the previous communication,[1] two different causes of the "α-effect" were suggested, the one depending on orbital overlap leading to electron repulsion, the other to some form of intramolecular catalysis. We consider here the reactions[2] of hydroxamic acids and their *N*-alkyl derivatives with acylating agents.

The extensive researches of Exner and his colleagues[3] have shown that hydroxamic acids ionise largely (> 90%) in the oximino-form (I),

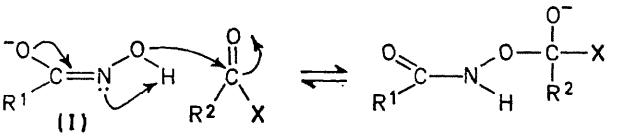


(I)

According to this structure, electron repulsion in the ground state should be negligible, and hence the anion probably reacts by a catalytic process. Reference to our previous work[4] on the mechanism of acylation of amidoximes,



suggests that (I), which is isoelectronic with an amidoxime, may react by a similar mechanism, *viz.*,



(I)

In support of this suggestion we find that the rate constants for the reactions of hydroxamate anions, amidoximes, and hydroxylamines with *p*-nitrophenyl acetate in water are related logarithmically to the pK_a of the corresponding conjugate acids (Figure). The same behaviour is observed

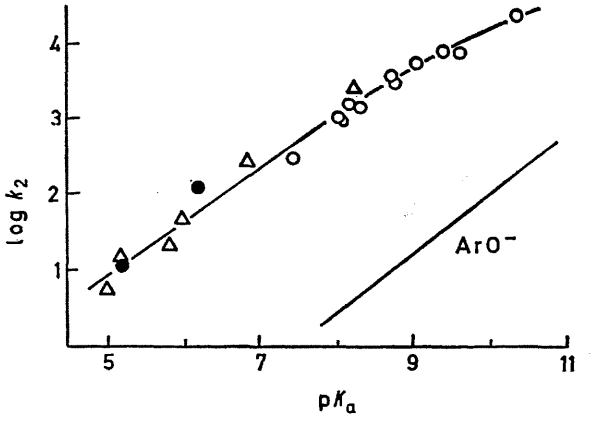


FIGURE. *log* k_2 *(bimolecular rate constant in* $M^{-1} \times min^{-1}$*) against* pK_a *of conjugate acid for the reactions of hydroxylamines* (●), *amidoximes* (△), *and hydroxamate anions* (○) *with* p-*nitrophenyl acetate in water at* 25°.

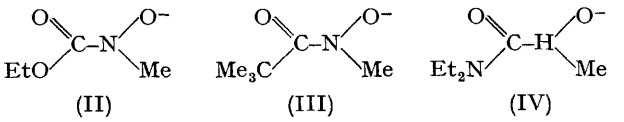
in reactions of benzoyl fluoride and ethyl chloroformate. Since these pK_a values refer to the protonation on nitrogen in each case, a relationship of this kind is to be expected for the suggested mechanism.

The *N*-substituted hydroxamic acids, which cannot tautomerise, ionise in the normal way,

$$R{\cdot}CON(Me)OH \rightleftharpoons \begin{matrix} O \\ \| \\ R-C-N \\ \quad\quad O^- \end{matrix}^{Me} + H^+$$

The enhanced reactivity of some of these acids must therefore be due to another factor. In view of the N–C=O conjugation, these acids and their anions would be planar, with the nitrogen lone pair in a p_π orbital. Repulsion between lone pairs on oxygen and nitrogen is possible and this may be the cause of the enhanced reactivity as discussed previously.[1]

In agreement with this explanation, it is found that anions (III) and (IV) do not show the "α-effect" although (II) does.



The "normal" reactivity of (III)† and (IV), and the comparatively high pK_a's of their conjugate acids (Table),

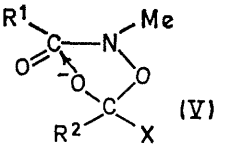
Rate enhancements in reactions of hydroxamate anions with p-*nitrophenyl acetate in water at* 25°

Hydroxamic acid		pK_a	Rate enhancement[a]
MeCO·N(Me)OH		8·84	105
EtO·CO·N(Me)OH	(II)	9·78	71
Me_3C·CO·N(Me)OH	(III)	9·94	2·2
Et_2N·CO·N(Me)OH	(IV)	11·2	2·1
MeCO·NHOH		9·37	191
Me_3C·CO·NHOH		9·59	126
EtO·CO·NHOH		10·35	112

[a] Defined as the ratio (bimolecular rate constant for hydroxamate anion/bimolecular rate constant for a phenoxide anion of the same basicity).

are attributed to steric hindrance, which removes the nitrogen from conjugation with the carbonyl group. This reduces the lone-pair repulsion since the nitrogen atom is then in the sp^3 hybridised form.

Alternatively the "α-effect" for these anions may be due to intramolecular catalysis (V) of a kind previously postulated for oximes.[5]



(V)

The "normal" reactivity of (III) and (IV) could then be explained by steric repulsion, preventing the formation of the cyclic transition state (V). No decision between these two mechanisms can be made at present.

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† The corresponding hydroxamic acid (non-substituted on nitrogen) shows the same enhanced reactivity as the other hydroxamic acids (Table).

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[2] B. E. Hackley, jun., R. Plapinger, M. Stolberg, and T. Wagner-Jauregg, *J. Amer. Chem. Soc.*, 1955, **77**, 3651; A. L. Green, G. L. Sainsbury, B. Saville, and M. Stansfield, *J. Chem. Soc.*, 1958, 1583; G. M. Steinberg and R. Swidler, *J. Org. Chem.*, 1965, **30**, 2362; W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1960, **82**, 1778; H. Kwart and H. Omura, *J. Org. Chem.*, 1969, **34**, 318.
[3] O. Exner and B. Kakac, *Coll. Czech. Chem. Comm.*, 1963, **28**, 1656; O. Exner, *ibid.*, 1964, **29**, 1337; O. Exner and J. Holubek, *ibid.*, 1965, **30**, 940; O. Exner and W. Simon, *ibid.*, p. 4078.
[4] J. D. Aubort and R. F. Hudson, *Chem. Comm.*, 1969, 1342.
[5] B. Miller, *J. Amer. Chem. Soc.*, 1962, **84**, 403; see also E. G. Sander and W. P. Jencks, *ibid.*, 1968, **90**, 6154.