Tetrahedron Letters No. 13, pp 1217 - 1220, 1972. Pergamon Press. Printed in Great Britain.

DUAL PARTICIPATION BY NEIGHBOURING OXIMATE ANION IN ELIMINATION AND CYCLIZATION OF MANNICH BASE OXIME SALTS

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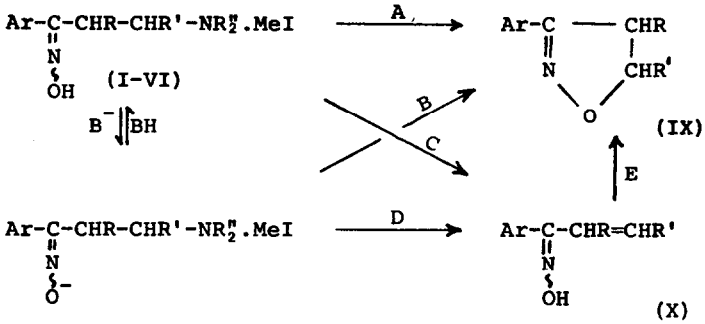
(Received in UK 7 February 1972; accepted for publication 17 February 1972)

The synthetic utility of Mannich base oxime salts (I-VI) to form either 2-isoxazolines or vinyl ketoximes upon reaction in basic media is dependent upon an understanding of the factors affecting the separate cyclization and elimination processes.[1] We now provide kinetic data for the competitive processes which rationalises previous work and demonstrates how the conditions may be altered to suit particular synthetic purposes.



(I,R,R'=H; $NR"_2$=NMePh. II,R=H; R'=Ph; $NR"_2$=NMe_2. III,Ar=Ph; R=H; R'=Ph; $NR"_2$=morpholino. IV,Ar=Ph; R,R'=H; $NR"_2$=NMe_2. V,Ar=Ph; R=Ph; R'=H; $NR"_2$=NMe_2. VI,Ar=Ph; R=H; R'=Me; $NR"_2$=NMe_2. VII,Ar=Ph,R,R'=H. VIII,Ar=Ph,R=H,R'=Ph).

Both the neutral oxime (path A) and the ionized oximate anion (path B) are possible nucleophilic species in cyclization;[2] similarly elimination may take place from either species presumably with different mechanistic consequences.[3] In aqueous base, cyclization of the Mannich base oximes (I) and (II) is the major reaction - the 2-isoxazolines (IX) being isolated in high yield (>90%). The fact that direct attack is occurring has already been demonstrated i.e. the cyclization does not involve path E or intermediate formation.[4] The pseudo first-order rate constants for cyclization of (I) and (II) are pH-independent at high pH but fall rapidly as the pH is decreased (e.g. below ca. pH 10). This behaviour corresponds to the involvement of the oximate anion as the nucleophilic species. This view is confirmed by the identity of pKa required to fit the kinetic data with spectrophotometric pKa's measured independently. Even at pH 8 neutral oxime attack (path A) is

Table 1: Rates of cyclization (k_c) and pKa's of the p-substituted phenyl oxime salts (I) and (II) in aqueous potassium hydroxide at 24.8°.

Oxime salts (I) p-subst.	MeO	Me	H	Br	NO_2
$10^2 . k_c(s^{-1})$	2.04	2.14	2.00	1.62	1.31
pKa	10.81	10.90	10.73	10.48	10.26
Oxime salts (II)					
$10^3 . k_c(s^{-1})$	3.52	4.06	3.33	2.54	2.02
pKa	10.86	11.02	10.66	10.60	10.41

Table 2: Rates of cyclization (k_c) and elimination (k_E) of the chain substituted oxime salts in 0.1M aqueous KOH at 24.8°.

Oxime Salt (configuration*)	IV *anti*	V,(2-Ph)*anti*	V,(2-Ph)*syn*	II,(3-Ph)*anti*	VI,(3-Me)*anti*
$10^4 . k_c(s^{-1})$	0.017	2.4	-	46	0.043
$10^4 . k_E(s^{-1})$	1.1	13	0.0095	0.9	0.38

Table 3: Amino leaving group variation in the oxime salts VII and VIII in 0.1M KOH at 24.8°.

Leaving group ($MeNR''_2$)	MeN⟨ ⟩	Me_3N	MeN⟨ ⟩O	$C_6H_5NMe_2$
pKa	10.08	9.76	7.41	4.85
$10^4 . k_c$ (VII)	0.0049	0.0175	0.73	196
$10^5 . k_E$ (VII)	9.80	11.4	14.8	15.0
$10^3 . k_c$ (VIII)	3.30	4.61	120	

Table 4: The effect of solvent/lyate ion change on the rates of cyclization (k_c) and elimination (k_E) of the oxime methiodides (*anti*) VII (R"=Me) in 0.1M lyate ion at 24.8°.

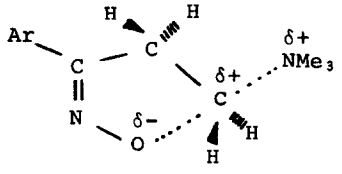
Solvent/lyate ion	H_2O/HO^-	$MeOH/MeO^-$	$EtOH/EtO^-$	i-PrOH/i-PrO^-	t-BuOH/t-BuO^-
$10^3 . k_c(s^{-1})$	0.00175	0.198	1.25	7.72	61.8
$10^4 . k_E(s^{-1})$	1.15	7.49	5.10	7.7	16.9

*The terms *syn* and *anti* refer to the relationship between 1-phenyl group and the oxime -OH.

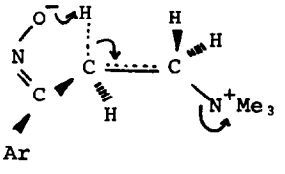
insignificant. The rates of cyclization of the anions (I) and (II) together with pKa data for these compounds are summarised in Table 1.

Substituent effects in Ar on the cyclization of the anion are small (ρ = -0.21 for (I) and = -0.28 for (II), using ordinary σ values[5]). The variation in pKa with substituent is more marked (ρ = 0.61 and 0.51 respectively)[6] showing that the substituent in the aryl ring is able to influence appreciably the charge density on the anion. The small substituent effect in cyclization is best explained therefore in terms of little O-C bond formation in the transition state for cyclization. This is consistent with the powerfully nucleophilic nature of the oximate anion.

The variation in the rates of cyclization (k_c) and elimination (k_E) with change in alkyl chain substitution in the Mannich base oximes is summarised in Table 2. In all cases substitution (by either Ph or Me α- or β to the oxime group) increased k_c. This is explicable in terms of a gem-effect which has previously been noted in cyclization reactions.[7] The substituent effects on k_E are also interesting, particularly when data for the *syn* and *anti* isomers of the 2-Ph compound V are compared. A 2-Ph substituent usually causes a 10^2 - 10^3-fold increase in elimination rate from 'onium compounds' (due to stabilization of the incipient carbanion[8]); we have observed a 10-fold increase for k_E on substitution of a Ph for H in the *anti* isomer. There is however a large difference (1400-fold) between the rates of eliminations of the *anti* and *syn* isomers of the oximes (Table 3).[9] There is precedent for smaller (i.e. 10^2-fold) rate differences in phosphonate ester hydrolysis where both *anti* and *syn* oximate groups participate (the latter more effectively) by intramolecular general base catalysis of nucleophilic water attack at a phosphorous centre.[10] It appears that the present case is unique in that the configurationally favourable *anti* oxime group is aiding the elimination process by intramolecular removal of the α-hydrogen (X).



IX



X

While the variation in nature of the leaving group causes a dramatic change in k_c (which increases by a factor of 10^4 when the pKa of the conjugate acid of the leaving group is decreased by ca. 5 units, see Table 3), k_E

remains essentially unchanged. The transition state of the two processes consequently are very different, C-$\overset{+}{N}$ bond breaking having substantially proceeded in the cyclization (IX) while in elimination little C-N stretching has occurred (X) i.e. the mechanism is on Elcb side of Elcb-E2 borderline.[11] This change in rate with the nature of the leaving group can be exploited synthetically to maximise either cyclization or elimination.[1]

The differences in the transition states for cyclization and elimination are also apparent from the individualistic variation of k_c and k_E with solvent/lyate ion (Table 4). While log k_c gives an excellent relationship with the Z values of Kosower (m^Z = -0.20, r = 0.999) indicating that the transition state (IX) involves charge dispersion, k_E, conversely, is almost independent of solvent, (m^Z = -0.05, r = 0.941). In this latter case, because there is little C-$\overset{+}{N}$ stretching in the transition state (X) the charge distribution does not differ greatly from that in the oximate substrate.

These kinetic results may be summarised as follows. The cyclization behaviour is consistent with direct participation of the oximate anion on developing electrophilic carbon centre sensitive to steric and electronic effects and to the nature of the solvent. The competing elimination is relatively insensitive both to the nature of the leaving amine and to reaction solvent. In both cyclization and elimination the oximate group plays a vital role - the favourable configuration (*anti*) alone gives cyclization products while this isomer also shows a greatly enhanced rate of elimination.

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