Tetrahedron Letters No.9, pp. 685-688, 1970. Pergamon Press. Printed in Great Britain.

AMBIDENT NEIGHBOURING GROUPS IV (1). THE INFLUENCE OF RING SIZE EFFECTS ON URETHANO ANCHIMERISM

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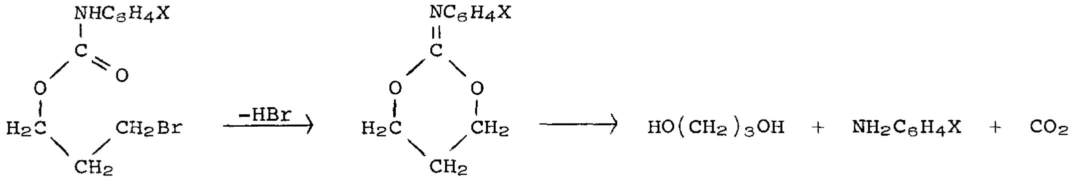
(Received in UK 14 January 1970; accepted for publication 21 January 1970)

We have outlined both the stereochemical (1) and kinetic (2) features of O-5 and N^--5 urethane closures but before these data can be used for generalised schemes of synthesis, some additional parameters are of interest. We examine one of these herein, namely the role of a neighbouring urethano function in six-membered ring closures, O-6 and N^--6. No systematic investigation of this ring-size question with ambident neighbouring groups has been reported previously in the literature.

We used as substrates the 3-bromopropyl-N-arylurethanes (I). Their O-6 reactions which took place in 80% aqueous ethanol, are outlined in Figure I. Table I summarises some of the relevant rate and thermodynamic data.



I

II

Figure I

Table I. Rates of O-6 cyclization of the halides p-$XC_6H_4NHCOOCH_2CH_2CH_2Br$ (I)

Substrate (I, X =)	10^6k_1, sec.$^{-1}$ (75°)	10^5k_1, sec.$^{-1}$ (100°)	$\Delta H^\ddagger$, kcal/mole	$\Delta S^\ddagger$, e.u.
C_2H_5O	19.4	14.2	19.7	-23.6
CH_3	16.9	13.4	20.5	-21.5
H	14.0	10.1	19.6	-24.7
Cl	9.9	7.9	20.7	-22.2
NO_2	1.7	1.4	20.9	-25.1

These data correspond to Hammett ρ values of -0.92 (r = 0.995, s = 0.084) at 75° (ρ for the corresponding O-5 reaction being -0.88) and ρ = -0.89 (r = 0.972, s = 0.081) at 100°. It is therefore clear that the change of substituent in the para position of the arylamine function affects the O-5 and O-6 closures to the same extent despite the greater remoteness of the reaction centre in the O-6 case. The rate spread observed with the compounds chosen (as the rather small ρ values would suggest) was small in both the O-6 and O-5 cases, with $k_{p\text{-}OC_2H_5}/k_{p\text{-}NO_2}$ (these being the relative rates for the p-ethoxy- and p-nitro-derivatives of I) = 11.6 (in the O-6 case) and = 9 (for the O-5 reactions). The thermodynamic data show the O-6 reaction series to be nearly isoenthalpic and thus to be entropy controlled, a feature which we comment on elsewhere (3). The entropies of activation for the O-6 change are, as expected (4), substantially (i.e. by 12-14 entropy units) more negative than the corresponding O-5 reactions.

Another interesting comparison between the five-membered and six-membered reactions is to compare the effect change in ring size has upon the closure of related pairs of compounds i.e. for homologous pairs. If we take the comparison between the most reactive member of each group, and the least reactive as well, we obtained the following ratios $k^*_{5\text{-}OC_2H_5}/k^*_{6\text{-}OC_2H_5} = 24$; $k^*_{5\text{-}H}/k^*_{6\text{-}H} = 24$; $k^*_{5\text{-}NO_2}/k^*_{6\text{-}NO_2} = 37$. In other words the five-membered closures are between 24 and 37 times faster than the six-membered. Capon (5) has tabulated the rates of ring-closure reactions as a function of ring-size for twenty different neighbouring groups and amongst the twenty, the nearest k_5/k_6 ratios to those we report are those for neutral -OH participation (in the cyclizations of $HO(CH_2)_{n-1}Cl$) with $k_5/k_6 = 25$, and neutral amino (in the cyclizations of $NH_2(CH_2)_{n-1}Br$) with $k_5/k_6 = 59$. Thus the combination of entropy and other effects built into these k_5/k_6 ratios seem strikingly similar in the case of the O-5 and O-6 urethano and hydroxyl closure.

In the presence of an equivalent of ethoxide ion compounds (I) undergo facile N^--6 closures to yield N-aryl oxazinid-2-ones (III), the relevant rate data being summarised in Table 2. As in the corresponding five-membered case (2) again we noticed a striking potentiation of the anchimerism by the urethane function in the presence of base, this facilitation being accompanied also by a change in the reaction-site of the ambident urethane

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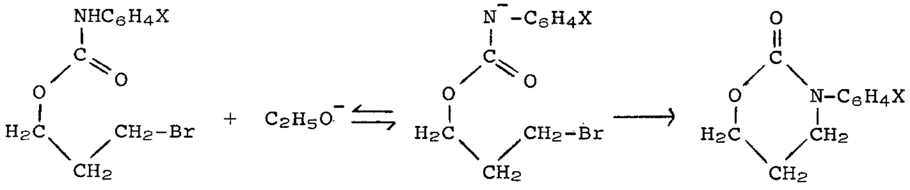
[*] These symbols represent the relative rates of ring closure with $p\text{-}X\text{-}C_6H_4\text{-}NHCOOCH_2CH_2Br$ (O-5 reactions) and $p\text{-}X\text{-}C_6H_4NHCOOCH_2CH_2CH_2Br$ (O-6 reactions) respectively.

anion (from O to N).



(I)

(III)

Figure 2

Table 2, Base-induced N^--6 reactions of Compounds (I)

Substrate (I, X =)	$10^4 k_2(0^\circ)$ $l.mole^{-1}sec.^{-1}$	$10^2 k_2(25^\circ)$ $l.mole^{-1}sec.^{-1}$	$\Delta H^\ddagger$ kcal/mole	$\Delta H^\ddagger$ e.u.
NO_2	50.6	23.4	24.1	+19.4
Cl	15.7	8.0	24.7	+19.4
H	5.9	2.7	24.1	+15.3
CH_3	5.5	2.4	23.8	+14.0
C_2H_5O	5.2	2.3	24.0	+14.5

The data in Table 2 correspond to Hammett ρ values of +0.93 (r = 0.982, s = 0.11) at 0° (the corresponding ρ for N^--5 urethane closure (2) being +1.74) and ρ = +0.95 (r = 0.985, s = 0.094) at 25° (N^--5 ρ = +1.72 at this temperature). There are two surprising effects in these data compared to those discussed for the O-6 closures. The first is the sharp reduction (essentially halving) of the ρ-values for N^--5 reactions by the change in ring size from five to six. The ambident base-induced reactions have in general composite ρ values, ρ_1 being that for the pre-equilibrium between substrate and its anion (ρ_1 being positive), and ρ_2 being that for the ring-closure of the substrate anion (ρ_2 being negative). For both the N^--6 and N^--5 processes $\rho_1 > \rho_2$. However, based on our O-6 vs O-5 data we would have expected ρ_2 for the N^--5 and N^--6 reactions to be close in value, with the result that the sharp reduction in overall ρ on changing from N^--5 to N^--6 should thus arise in a reduction in ρ_1 values. This also seems unlikely. We are seeking further systems to clear up this anomaly.

In contrast to the ρ changes just discussed, change in ring size leaves the overall base-rates essentially unchanged, with k_{5-NO_2}/k_{6-NO_2} (using the symbolism as used above) = 5, k_{5-H}/k_{6-H} = 1.7, $k_{5-OC_2H_5}/k_{6-OC_2H_5}$ = 1.2 Looking again at Capon's tabulation (5), the oxygen participation system (namely the cyclization of $^{-}O(CH_2)_nCl$) does not correspond to our data, (k_5/k_6 for the O^- case being 1000). Instead, the cyclizations of carboxylate ion $^{-}OOC(CH_2)_nCl$, which resemble our systems even more closely in structure, show a similar ratio, (k_5/k_6 being 1.1). As was the case with the N^--5 series, thermodynamic data in Table II (which again are composite) show the base-runs to be isoenthalpic, the overall process being entropy controlled (3). Increase in ring-size from N^--5 to N^--6 makes the entropy changes more negative by 4-5 entropy units.

The products of both reactions we have discussed above namely the O-6 and N^--6 closures were consistent with the reactions formulated. In the O-6 case we isolated the corresponding amines (II) (as picramides) in yields between 80-95% and in the N^--6 cases, the N-aryl oxazinid-2-ones (III) were isolated in excellent yields (between 90 and 99%) in all cases.

This work was carried out during the tenure by one of the authors (DFF) of a State Maintenance Allowance for Research.

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