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MECHANISMS OF NUCLEOPHILIC SUBSTITUTIONS AT UNSATURATED CARBON. LEAVING-GROUP EFFECT IN THE REACTIONS OF PIPERIDINE WITH VARIOUS 2-X-TROPONES

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Though nucleophilic substitutions on tropone derivatives carrying displaceable groups at the ring positions have been well explored from the preparative standpoint [1] few mechanistic studies are available and mechanisms have been mainly inferred from product analysis.

We felt that these reactions deserve more attention from the standpoint of kinetic measurement since at present no comparison is possible with formally related reactions such as nucleophilic substitutions at the carbonyl carbon or at the activated aromatic carbon. Thus, to enlarge our knowledge of nucleophilic substitutions at unsaturated carbon we started a systematic study and report here some data concerning the reactions of piperidine with 2-X-tropones (X= chlorine, bromine, iodine or methoxyl) in benzene to give 2-piperidinotropone ** quantitatively.

Deuterium labelling at the 3,5,7-positions of the tropone ring[2] shows (^{1}H n.m.r. analysis) that these reactions involve direct displacement of the leaving-group, no detectable attack by piperidine at the 7-position[2a] occurring. Kinetic data, obtained on following formation of 2-piperidinotropone by ultraviolet analysis, are fitted by equation (1) (where PIP stands for piperidine). The values of k_{PIP}/k_o are ca. 3 mole^{-1}l. for both the chloro-

$$\text{Rate}/[\text{2-X-tropone}][\text{PIP}] = k_o + k_{PIP}[\text{PIP}] \qquad (1)$$

and the bromo-compound, ca. 15 for the iodo-compound, and ca. 0.02 for the methoxy-compound at 25°. Activation free energies are about the same for both the k_o and the k_{PIP} part of equation (1) and, moreover, they vary very little

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**M.p. 57°C. Satisfactory elemental analysis and ^{1}H n.m.r. spectra were obtained.

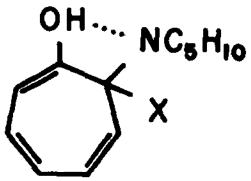
with changing the leaving-group.

Investigation of the temperature dependence of the rate revealed itself very informative. In fact, these reactions are not genuinely insensitive to the nature of the leaving-group as the invariance of the activation free energy is due to these reactions following an isokinetic relationship with an isokinetic temperature near the working temperature. This is shown in the figure and is further substantiated by a reasonably linear $\Delta F^{\ddagger}$ vs $\Delta H^{\ddagger}$ plot[3] (not shown) which can be obtained from the data in the Figure.

Examination of the Figure reveals that there is a relationship between activation entalpy and bond energy of the bond with the leaving-group in the substrate. In fact, that parameter containing potential energy terms ($\Delta H^{\ddagger}$) increases notably with increasing energy of the carbon-leaving-group bond in the substrate.

It is commonly felt that isokinetic relationships point to a sameness of mechanism within the reactions correlated.[4] As concerns the mechanism of the present class of reactions a two-step mechanism <u>via</u> a tetrahedral intermediate (I) had been invariably considered as the most likely one.[1,5] This mechanism has

(I)



a close resemblance with the nucleophilic S_N2 displacement at the carbonyl carbon[1,5] or with the addition-elimination mechanism of nucleophilic aromatic substitution.[6] Although peripheral information makes the two-step mechanism very appealing, the relationship with the nucleophilic substitutions at the other unsaturated carbon atoms are not supported by the present results. In fact, the activation free energies of the S_N2 nucleophilic substitution at the carbonyl carbon are known to be strongly affected by the nature of the leaving-group either in protic[7] or in non-polar non-protic solvents.[8] On the other hand in activated aromatic substitution chlorine, bromine, and iodine are displaced at nearly the same rates owing to a sameness of activation parameters while methoxyl is very resistant to displacement.[9]

Another important difference lies in the timing of the proton transfer. In fact, when the nucleophile is a protic amine, displacement of a poor leaving-group like methoxyl requires strong base catalysis either in aromatic nucleophilic substitution or in nucleophilic substitution at the carbonyl carbon.[9,10] Here, to the contrary, displacement of methoxyl gives rise to nicely first-order kinetics with respect to piperidine. Moreover, oddly enough, the ratio of rate coefficients k_{PIP}/k_o, which can be taken as a measure of the extent of base catalysis, is higher for a good leaving-group as iodine than for methoxyl.

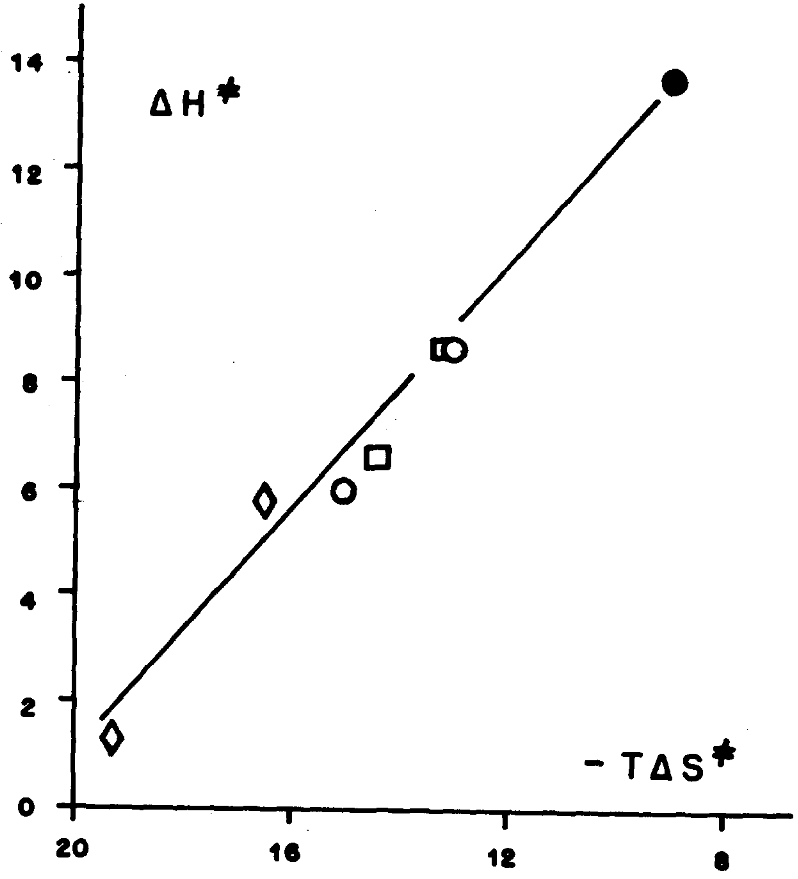


FIGURE. Plot of $\Delta H^{\ddagger}$ vs $-T\Delta S^{\ddagger}$, kcal mole^{-1}, for the reactions of piperidine with (●) 2-methoxy-, (○) 2-chloro-, (□) 2-bromo-, and (◇) 2-iodo-tropone in benzene. Lower values of $\Delta H^{\ddagger}$ are for the k_{PIP} terms. The straight line is drawn for the isokinetic temperature 340°K.

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