Tetrahedron Letters No.53, pp. 5505-5508, 1968. Pergamon Press. Printed in Great Britain.

KINETIC HYDROGEN ISOTOPE EFFECTS IN THE PIPERIDINO DEHALOGENATION OF HETEROAROMATIC SUBSTRATES+

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(Received in UK 10 September 1968; accepted for publication 1 October 1968)

There are two major points of interest related to the mechanism of the aromatic substitution reactions with primary and secondary amines as the nucleophilic reagents, i.e., the base-catalysis and the hydrogen isotope effect. The latter effect was encountered but seldom and received less systematic attention. So far no study has been heretofore reported dealing with N-heteroaromatic substrates. In connection with our current investigations on the aza-group activation and on the leaving group effect, we have examined the kinetic hydrogen isotope effects involved in the piperidino dehalogenation of some simple 2- and 4-fluoro and chloroquinoline derivatives in neat piperidine or N-deuteriopiperidine as solvents. The data are collected in the Table. The isotope effects, as expressed by the k_H/k_D ratios, are absent or negligible if the leaving group is Cl, at either α- or γ-position; they are small and positive if the leaving group is F at the γ-position, and, again, negligible when F is at the α-position. The observed effects are not secondary effects caused by a change in nucleophilicity of the piperidine, because in such a case an inverse isotope effect would be obtained (1).

From the point of view of the size of the effects, the present results are similar to those found with nitro-activated systems where the isotope

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+ Nucleophilic Heteroaromatic Substitution. XXX. Presented at the 5. Arbeitstagung über stabile Isotope (Leipzig, October 22-29, 1967). For part XXIX, see G. Illuminati and F. Stegel, Tetrahedron Letters, 4169 (1968).

TABLE

Kinetic Hydrogen Isotope Effects in the Piperidino Dehalogenation Reaction of Some Halogenoquinolines in Piperidine•

Quinoline Derivative	t°C	$10^5 \times \underline{k}_H$••	$10^5 \times \underline{k}_D$••	$\underline{k}_H/\underline{k}_D$
2-Chloro	86.5	3.15	3.20	0.985
4-Chloro	86.5	0.0859	0.0857	1
4-Chloro-2-methoxy	86.5	0.0285	0.0293	0.972
4-Fluoro-2-methoxy	86.5	0.396	0.317	1.25
	100.0	0.796	0.638	1.25
4-Fluoro-2,8-dimethyl	120.0	0.583	0.488	1.20
2-Fluoro-4-methoxy	50.8	1.53	1.46	1.05

• Piperidine-1-d was at least 95% deuteriated, as checked by N.M.R.. H_2O content in piperidine: 0.024 M; D_2O content in piperidine-1-d: 0.028 M

•• $\underline{k}$ in $M^{-1}sec^{-1}$. The kinetics were followed by halide ion analysis. The experimental error was about 2% and 3% for the dechlorination and defluorination reactions, respectively.

effects are also usually small (2,3) or absent (4,5). Nevertheless, they show some new features, which are relevant to the reaction mechanism.

a) The isotope effects are obtained at the highest concentration of base (neat piperidine).

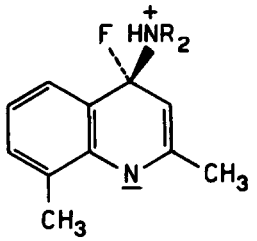
b) The isotope effects, though small, yield a direct comparison of several substrates under identical conditions; in particular, they show two cases of dependence on the structure of the substrate, i.e., the one related to the leaving group (Cl vs. F) and the other to the position of the reacting center (α vs. γ).

In the general formulation of the two-stage mechanism proposed for these reactions (6)

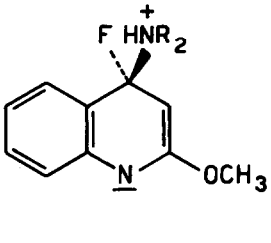
$$Ar - X + Nu \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \sigma\text{-adduct} \xrightarrow{k} \text{products}$$

a kinetic isotope effect is possible if the proton transfer from the σ-adduct (I) to the medium in the second stage of the reaction is involved in the rate-limiting step. Here $\underline{k}$ is an over-all symbol for diverse modes of

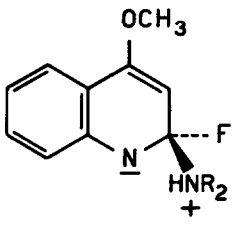
decomposition, some of them implying base-catalyzed paths. Since our data



Ia



I b



II

refer to a constant excess of reagent and base (piperidine), we can use the following simplified expression for the steady-state treatment,

$$\text{rate} = \frac{k_1 k[\text{substrate}]}{k_{-1} + k}$$

Kinetic hydrogen isotope effects can be observed under the condition $k_{-1} >> k$. They are expected during the decomposition of the σ-adduct, either in a preliminary slow proton transfer followed by rapid expulsion of the leaving group or in a concerted process in which N-H and C-X bond-breaking are simultaneous. The finding that the isotope effect at the γ-position depends on the nature of the halogen and is higher for the poorer leaving group (F) would support a concerted mechanism of some kind in which the relative importance of C-X and N-H bond-breaking, in the elimination process of X--C-N--H, is a function of X. In nitro-activated substrates, where isotope effects are absent when the leaving group is halogen, with only one exception (3), small effects are found with still poorer leaving groups (OR).

By combining the data in the literature with the present results, the tendency for the kinetic hydrogen isotope effect to occur would seem to increase in the order OR > F > Cl, which is opposite, as expected, to the order of ease of detachment of the groups from saturated carbon (7).

The C-X bond-breaking in the σ-adduct must depend on the polar effect of the other substituent attached at the geminal carbon atom and should be made easier by a decrease in the positive charge of the quaternized nitrogen. At the α-position, such a decrease may take place by the electrostatic interaction between opposing, adjacent charges (II). This will then cause the leaving group to depart in a less concerted way resulting in no isotope effect, as is observed. The disappearance of the isotope effect on going from the γ- to the α-position and the solvent α-aza effect described

elsewhere (5) would thus have very much the same origin and be, therefore, mutually consistent. The participation of the ammonium proton in an intramolecular process for the reaction of the α-halogeno derivative may play a role but is still an open question (5).

Some of the proposed detailed mechanisms (6) may explain why base catalysis often is not accompanied by a kinetic hydrogen isotope effect. The fact that such an effect does appear from time to time in a significant way may mean that several mechanistic situations, rather than a single one, are possible depending on the diverse experimental variables that characterize a given reaction. The definition of the scope of such situations should possibly be obtained from a more extensive knowledge of the correlations of the kinetic hydrogen isotope effect with base catalysis in nucleophilic aromatic substitutions with amines.

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