the reactions of 1,2-bis(3-carboxyacryloyl)hydrazine and 1-benzenesulfenyl-2-(3-carboxyacryloyl)hydrazine with boiling thionyl chloride.[3] The result is also in accord with the preparation of *N*-phenyl, *N*-(*p*-nitrophenyl), and *N*-(*m*-nitrophenyl) derivatives of α-chlorosuccinimide.[6]

Generally, the addition of hydrogen chloride to N-substituted maleimides is expected to be slower than addition to the corresponding maleamoyl chlorides suggested in Scheme I. However, substituents on the nitrogen of the maleimide would have a great effect on the rate of addition of hydrogen chloride. Such an effect would be opposite to the conclusions mentioned above regarding the addition to N-substituted maleamoyl chloride (Scheme I).

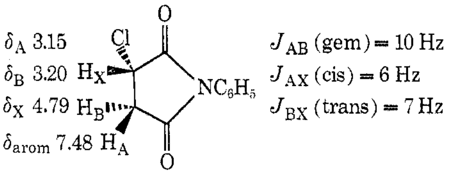
It appears that thionyl chloride may form N-substituted maleisoimides provided that the products are highly stabilized. The bismaleisoimide, prepared by Feuer,[4] seems to be the first maleisoimide reported from the dehydration of maleamic acids with thionyl chloride.

Chloroacetyl chloride reacted with *N*-phenylmaleamic acid in the presence of 1 molar equiv of triethylamine at 0–5°, forming *N*-phenylmaleisoimide in 54% yield.[8] When 2 molar equiv of triethylamine was employed, the product was only *N*-phenylmaleimide, no isoimide being detected in the infrared spectrum of the compound. These results are in agreement with previously suggested mechanism.[1a]

Experimental Section

Preparation of Maleamic Acids.—The procedures used here were similar to those in a previous work.[1a]

Reaction of *N*-Phenylmaleamic Acid with Thionyl Chloride in Presence or Absence of Triethylamine.—To a solution of 0.025 mol of *N*-phenylmaleamic acid in 100 ml of methylene chloride, 0.025 mol of triethylamine was added. The mixture was cooled in an ice bath to 0.5°. Thionyl chloride (0.025 mol) was added dropwise during 5 min, after which stirring was continued for 10 min. A violent reaction and fuming was observed at the beginning and an orange solution formed. The mixture was filtered from a small amount of triethylamine hydrochloride and the filtrate was stirred with excess dilute sodium bicarbonate solution for 50 min. The methylene chloride layer was then washed with water and dried with anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The orange-yellow solid that remained was recrystallized from boiling water to obtain 0.2 g (26%) of α-chloro-*N*-phenylsuccinimide, mp 118–119°. Ir (CCl_4) showed C═O absorption at 1728 cm^{-1} and no absorption was observed around 1650 cm^{-1}, indicating the absence of a carbon–carbon double bond. The nmr spectrum showed an ABX-type pattern as follows.[9]



Using excess triethylamine in this reaction resulted in a 40% yield of α-chloro-*N*-phenylsuccinimide when the reaction was conducted at 25°. When *N*-phenylmaleamic acid was allowed to react with excess thionyl chloride at 40°, the yield was 50%. The optimum yield (57%) was obtained when the last mixture was refluxed for 0.5 hr. When the amic acid and 1 equiv of thionyl chloride were allowed to react at −20° (Dry Ice–acetone bath), the product was *N*-phenylmaleimide (9.5% yield), mp 88° (lit.[10] mp 89–89.8°).

Reaction of Thionyl Chloride with *N*-Phenylmaleimide in Presence of Water.—In a three-necked flask *N*-phenylmaleimide[10] (0.01 mol) and thionyl chloride (0.01 mol) in 40 ml of methylene chloride were stirred and warmed to about 30°. Water (0.01 mol) was then added drop by drop. A violent reaction occurred in the beginning and hydrogen chloride was evolved, but without any change in the color of the solution. The solution was washed with water and dried with anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was unchanged *N*-phenylmaleimide, mp 88–89°.

Separation of *N*-(*p*-Methoxyphenyl)maleimide from α-Chloro-*N*-(*p*-methoxyphenyl)succinimide.—The solid yellow product left from refluxing thionyl chloride with *N*-(*p*-methoxyphenyl)-maleamic acid was dissolved in alcohol by heating, filtered, and cooled. A white precipitate was obtained by filtration. When the filtrate was evaporated, yellow crystals of *N*-(*p*-methoxyphenyl)maleimide were obtained, mp 148° (lit. mp 148–149°).[7] This last compound showed the presence of chlorine on sodium fusion, while the corresponding imide did not.

Anal. Calcd for $C_{11}H_{10}O_3NCl$: C, 55.12; H, 4.21; N, 5.84. Found: C, 55.27; H, 4.03; N, 5.64. *Anal.* Calcd for $C_{11}H_9O_3N$: C, 65.02; H, 4.43; N, 6.89. Found: C, 65.11; H, 4.42; N, 6.77.

Registry No.—Thionyl chloride, 7719-09-7; chloroacetyl chloride, 79-04-9; *N*-phenylmaleamic acid, 555-59-9; *N*-propylmaleamic acid, 36342-07-1; *N*-ethylmaleamic acid, 4166-67-0; *N*-(*p*-methoxyphenyl)maleamic acid, 24870-10-8; *N*-(*p*-nitrophenyl)maleamic acid, 36342-10-6; 2-chloro-*N*-phenylsuccinimide, 36342-11-7; *N*-phenylmaleimide, 941-69-5; *N*-(*p*-methoxyphenyl)maleimide, 1081-17-0; 2-chloro-*N*-(*p*-methoxyphenyl)succinimide, 36342-13-9.

Acknowledgment.—The author is grateful to the College of Pharmacy, University of Baghdad, for providing space, reagents, and equipment.

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(8) For experimental procedure see ref 1a.

(9) The coupling constants were calculated according to A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969.

(10) *Org. Syn.*, **41**, 94 (1961).

The Bromination of Perdeuterionaphthalene[1]

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Received August 7, 1972

Aromatic bromination is known to proceed by the two-step sequence shown.

$$\mathrm{ArH + Br_2 \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ArHBr^+ + Br^-}$$

$$\mathrm{ArHBr^+ \xrightarrow{k_2} ArBr + H^+}$$

If the first step is rate controlling ($k_2 \gg k_{-1}$), the observed rate constant varies with bromide ion concentration according to the equation $k_{\mathrm{obsd}} = k_1K/(K + \mathrm{Br}^-)$ (eq 1), where K is the dissociation constant of the tribromide ion and k_1 the true rate constant of bromination by free, uncomplexed bromine.[3] If the second step is partially or completely rate determining, a different dependence on bromide ion is obtained.[4,5] In

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(1) Kinetics of Aromatic Halogenation. XIII.

(2) Taken from the M. A. Thesis of Albert Ehrlich, Bryn Mawr College, 1969.

(3) E. Berliner and M. C. Beckett, *J. Amer. Chem. Soc.*, **79**, 1425 (1957).

(4) E. Berliner, J. B. Kim, and M. Link, *J. Org. Chem.*, **33**, 1160 (1968).

(5) B. T. Baliga and A. N. Bourns, *Can. J. Chem.*, **44**, 363, 379 (1966).

almost all cases conducted in aqueous acetic acid eq 1 is satisfied.[6] Consequently, no significant deuterium isotope effects, and no base catalysis, have been observed in bromination,[7] except when the position of substitution is sterically crowded.[8]

An isotope effect, if obtained, should increase with the bromide ion concentration, because the latter will affect the reversal of the first step, and lead to the condition k_{-1} (Br^-) $\gg k_2$, on which the isotope effect depends. In an earlier investigation of the bromination of 4,4′-dideuteriobiphenyl, the bromide ion concentration was varied only slightly, and the small, invariant isotope effect observed was interpreted as a secondary isotope effect.[9]

We now report the bromination of perdeuterionaphthalene (octadeuterionaphthalene) in 50% aqueous acetic acid in which the bromide ion concentration was varied over the wider range 0.1–0.8 *M* at a constant ionic strength of 0.8 *M* ($NaClO_4$). The bromination of naphthalene had previously been studied at an ionic strength of 0.5 *M*,[3] and this study was repeated at the higher ionic strength. Results are shown in Table I.

Table I

The Bromination of Naphthalene and Perdeuterionaphthalene in 50% Aqueous Acetic Acid[a,b]

[NaBr], mol/l.	[NaClO$_4$], mol/l.	$(10^2 k_{obsd})_H$	$(10^2 k_{obsd})_D$	$(k_{obsd})_H/(k_{obsd})_D$
0.10	0.70	6.44	7.88	0.817
0.20	0.60	3.68[c]	4.25	0.866
0.30	0.50	2.50	2.84	0.880
0.40	0.40	1.99	2.13	0.934
0.50	0.30	1.59	1.66	0.958
0.60	0.20	1.31	1.36	0.963
0.70	0.10	1.13	1.12	1.01
0.80	0.00	0.974	0.973	1.00

[a] Naphthalene ≅0.007 *M*, perdeuterionaphthalene ≅0.005 *M*, $Br_2 \simeq 0.002$ *M*, temperature 24.9°. [b] All rate constants are in l. mol^{-1} sec^{-1}. [c] A value of 3.64×10^{-2}, obtained under the same conditions, is reported in ref 3.

As shown earlier, the bromination of naphthalene follows eq 1, and so does the bromination of perdeuterionaphthalene (Figure 1). The bromination of fully deuterated naphthalene therefore obeys the same rate law as naphthalene, and the first step must be rate controlling ($k_2 \gg k_{-1}$). The true rate constants (the least-squares slopes in Figure 1) are 0.474 ± 0.005 for naphthalene[10] and 0.572 ± 0.002 l. mol^{-1} sec^{-1} for deuterionaphthalene. The ratio $(k_1)_H/(k_1)_D$ is 0.829 and the reaction has a secondary inverse isotope effect.

The data in Table I reveal that the isotope effects at different bromide ion concentration actually increase with bromide ion concentration (last column in Table I). This could be interpreted to mean that there is indeed a slight return of the intermediate to reactants, and that at sufficiently high bromide ion concentration a positive isotope effect might be obtained. By methods used earlier,[4,5] one can then calculate that the reversibility ratio $(k_2/k_{-1})_H$ is 13.0,[11] and the ratio $(k_2/k_{-1})_D = 3.48$. The extent of return thus calculated is only very small. For every molecule of intermediate that returns to reactants, 26 go on to form products in the case of naphthalene, and seven in the case of perdeuterionaphthalene at a 0.5 *M* bromide ion concentration. It is sufficiently small that eq 1 is hardly perturbed.[12] As expected, a peri hydrogen in naphthalene provides much less steric crowding in the intermediate than a peri-methyl group, because in the bromination of 1,5-dimethylnaphthalene, only one molecule of intermediate goes on to products for every eight that return.[4] The ratio of C–H to C–D bond breaking, k_{2H}/k_{2D}, the isolated primary isotope effect, which would be observed if the second step were fully rate controlling, is calculated to be 3.74.[13]

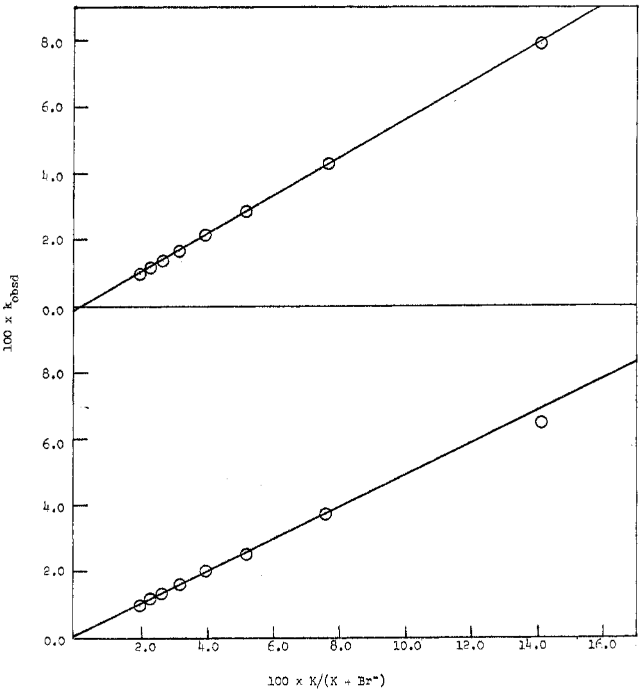

Figure 1.—The dependence of the rate of bromination on the bromide ion concentration: lower line, naphthalene; upper line, naphthalene-d_8.

The possibility, however, also exists that this trend in individual rate constants, or part of the trend, is a kinetic artifact caused by the high ionic strength of the medium. If eq 1 were to hold strictly, the lines in Figure 1 should pass through the origin. The line for naphthalene has a small positive intercept, $(6.93 \pm 2.15) \times 10^{-4}$, which has been interpreted as being due to a small amount of bromination by the tribromide ion.[3] The line for deuterionaphthalene has a small negative intercept of $(-1.49 \pm 0.16) \times 10^{-3}$ which has no physical significance. It is likely that NaBr and $NaClO_4$ do *not* have the same effect on the ionic strength of the medium and on the activities of naphthalene and deuterionaphthalene, and it is possible that the difference in the intercepts, and hence the trend, or part of the trend, in the individual k_H/k_D values is due to this effect. The deviation (negative intercept) is in the direction expected if the condition in footnote 12 does

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[6] L. Altschuler and E. Berliner, *J. Amer. Chem. Soc.*, **88**, 5837 (1966); U. P. Zimmerman and E. Berliner, *ibid.*, **84**, 3953 (1962); E. Berliner and J. C. Powers, *ibid.*, **83**, 905 (1961); E. Berliner and B. J. Landry, *J. Org. Chem.*, **27**, 1083 (1962).

[7] E. Berliner, *Progr. Phys. Org. Chem.*, **2**, 253 (1964); H. Zollinger, *Advan. Phys. Org. Chem.*, **2**, 163 (1964).

[8] P. C. Myhre, *Acta Chem. Scand.*, **14**, 219 (1960); E. Helgstrand, *ibid.*, **19**, 1583 (1965); E. Helgstrand and A. Nilsson, *ibid.*, **20**, 1463 (1966).

[9] E. Berliner and K. E. Schueller, *Chem. Ind.* (*London*), 1444 (1960).

[10] Compared to 0.341 l. mol^{-1} sec^{-1} at an ionic strength of 0.5 *M*.

[11] Only the five points at higher bromide ion concentration were used.

[12] This means that the bromide ion concentration is almost negligible relative to the term k_2/k_{-1} in the steady-state equation. See eq 3 in ref 4.

[13] The usual assumption is made that $(k_{-1})_H = (k_{-1})_D$.

not hold, which will be more the case for napththalene-d_8 than for napththalene, because $(k_2/k_{-1})_H > (k_2/k_{-1})_D$. This would seem to argue in favor of the former interpretation.

There is no ambiguity about the inverse isotope effect in the first step. According to Streitwieser and coworkers,[14] secondary inverse isotope effects can be caused by the rehybridization of the carbon–hydrogen bonding orbitals from sp^2 to sp^3, which are, however, often compensated by hyperconjugation in the transition state which leads to the intermediate. An additional factor ought to be of importance in the present instance. Because of anharmonicity effects, C–D bonds behave as if they were more electron releasing than C–H bonds.[15] The inductive effect of seven C–D bonds not involved in the reaction must combine with the rehybridization effect to more than compensate for the rate-decreasing effect of hyperconjugation and thus lead to the inverse isotope effect observed here.

Experimental Section

Materials and kinetic procedures were as described before.[3] A sample of naphthalene was recrystallized five times from ethanol and had mp 80.1–80.5° (corrected). The sample of naphthalene-d_8, obtained from Merck Sharpe and Dohm of Canada Limited, was recrystallized three times and had mp 79.6–80.2°. Its nmr spectrum showed no indication of incomplete deuteration. The rate constants listed in Table I are averages of at least two runs. More runs were conducted if average runs differed by more than 2%.

Registry No.—Perdeuterionaphthalene, 1146-65-2; naphthalene, 91-20-3.

Acknowledgment.—This work was supported by National Science Foundation Grant GP-4986, which is gratefully acknowledged.

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Hydrogen–Deuterium Exchanges in Pyrimidine *N*-Oxides

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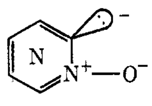
Received May 19, 1972

Acid- and base-catalyzed H → D exchange processes in pyridine *N*-oxides,[1] pyrazine *N*-oxides,[2] and pyridazine *N*-oxides[3] have been the subject of several recent papers.

The general conclusions that can be drawn from these studies are as follows.

(1) The hydrogens on the carbon atom α to the *N*-oxide group are much more readily exchanged under base catalysis than are any of the other ring protons.

(2) The exchange process occurs *via* "anionic ylides" such as depicted by structure **1**.



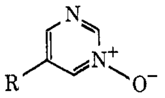
1

(3) The replacement of a ring =CH function in a pyridine *N*-oxide by a =N atom has a dramatic rate-enhancing effect on these exchange reactions.

This pattern is significantly different from that observed in the nonoxidized parents of these compounds where the hydrogens α to the ring nitrogen atom exchange *less* readily than do the other ring protons.[4–6] (The relative $H_2:H_4:H_5$ exchange rates in pyrimidine, for example, are 1:3.25:46.7). A comparison of the α-proton exchange rate in pyridine with those in pyrimidine and in pyrazine show that the latter two compounds undergo this exchange 100 times as readily. An even more dramatic increase is noted when the α-proton exchange rate in pyridine is compared with that observed in pyridazine, where the latter exchanges 1000 times as readily as the former.

Zoltewicz and coworkers[6] have suggested that the rate difference between the exchange of α protons and those further removed from the ring nitrogen atom is due to a decreased s character of the carbon–hydrogen bond adjacent to the sp^2 nitrogen atom and the repulsive interaction between the electron pairs on nitrogen and the (developing) carbanion.

In an effort to delineate the effect that sp^2 nitrogen atoms have upon the H → D exchange rates of "azapyridine *N*-oxides" we have now examined the behavior of several 5-substituted pyrimidine 1-oxides when they are subjected to base-catalyzed H → D exchange (Table I). In these *N*-oxides (**2a–e**) we expect H-2 as well as H-6 to exchange.



2a, R = H
b, R = CH_3
c, R = Br
d, R = OCH_3
e, R = $N(CH_3)_2$

The second-order rate constants, determined as described in the previous paper of this series,[2] for H-2 and H-6 of pyrimidine *N*-oxide (2a) are 1.8×10^{-3} and 4.7×10^{-2} l. mol^{-1} min^{-1}, respectively. Thus, H-6 exchanges 26 times as rapidly as does H-2, while both of these protons exchange much less readily than do H-2 and H-6 in pyrazine 1-oxide (0.16 l. mol^{-1} min^{-1}). Thus, the nonoxidized nitrogen atom, when situated ortho or para to the exchanging proton, is much less effective in faciliting H → D exchange than when it is located meta to the exchanging position.

Zoltewicz and coworkers[6] have shown that in the diazines themselves the activating effects of the sp^2 nitrogen atoms are in the order para ≈ meta ≫ ortho. This positional reactivity differs from that found in

[1] J. A. Zoltewicz and G. M. Kauffman, *Tetrahedron Lett.*, 337 (1967).

[2] W. W. Paudler and S. A. Humphrey, *J. Org. Chem.*, **35**, 3467 (1970).

[3] Y. Kawazoe, Y. Yoshioka, M. Yamada, and N. Igeta, *Chem. Pharm. Bull.*, **15**, 2000 (1967).

[4] J. A. Zoltewicz and C. L. Smith, *J. Amer. Chem. Soc.*, **89**, 3358 (1967).

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[6] J. A. Zoltewicz, G. Grahe, and C. L. Smith, *J. Amer. Chem. Soc.*, **91**, 5501 (1969).