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PHOTOCHEMICAL AROMATIC HYDROXYLATION BY AROMATIC AMINE N-OXIDES: REMARKABLE SOLVENT EFFECT ON NIH-SHIFT

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Summary : Photooxygenations of 4-^{2}H-anisole (3) and o-xylene (5) by 3-methylpyridazine 2-oxide (1) or pyridine 1-oxide (2) were studied in a variety of solvents at varying irradiation temperatures. Remarkable solvent effect on NIH-shift coupled with their hydroxylation processes was observed.

Photolysis of aromatic amine N-oxides has been known to represent one of the most satisfactory mechanistic models of biological oxygen-atom transfer reactions catalyzed by monooxygenases[1]. In the preceeding paper we suggested that the oxygen transfer reactions by the N-oxides should involve generation of oxene (atomic oxygen) as the reactive species[2]. On the other hand, reactions of ground state oxygen-atom, O(^{3}P), with organic compounds have been extensively studied in the gas phase[3], and also, recently, in condensed phases such as photolysis of ozone in liquid N$_2$[4], microwave discharge of O$_2$ or of N$_2$O and N$_2$[5a-c] and γ-radiolysis of liquid CO$_2$[6a-c]. Of these reactions, their aromatic hydroxylations have been studied in detail and their reaction modes were discussed as the models of biological hydroxylations as well. Therefore, such reactions by photolysis of aromatic amine N-oxides were compared with those of O(^{3}P) atom generated by the methods mentioned above.

3-Methylpyridazine 2-oxide (1) and pyridine 1-oxide (2) were irradiated in the presence of 4-^{2}H-anisole (3)[7] in a variety of solvents including 3 itself at varying temperatures[8]. Formation ratios of ortho, meta and para-hydroxyanisoles and ^{2}H retention values in para-hydroxyanisole (4) (NIH-shift[9]) in each irradiation were determined by gas chromatography (5 % Advance-DS, 1.5 m) and GC-MS (5 % Advance-DS, 1 m), respectively, and the results are summarized in Table 1 and 2.

Table 1 shows the electrophilic charactor of the oxidant generated by this method, which was demonstrated also in reported reactions of O(^{3}P). Relatively large ortho/para ratios(2-4) indicate little or no steric hinderance to the reaction ortho to methyl group, it being consistent with our previous conclusion suggesting that the reactive species involved in this oxygen transfer reaction should be atomic oxygen rather than excited N-oxides or their rearrangement products. In this reaction ratios of meta substitution are somewhat higher compared with the reported reactivities of O(^{3}P)[2b,5c], and it might indicate partial contribution of some other oxidant.

The results listed in Table 2 demonstrated a remarkable solvent effect on ^{2}H retention values in para hydroxylations by both 1 and 2, and the values were found to increase with solvent polarity[10] except the cases in benzene and in anisole. As another feature of the reaction, higher retention values were generally observed at higher temperatures. This observation is inconsistent with the results obtained in the

Scheme 3

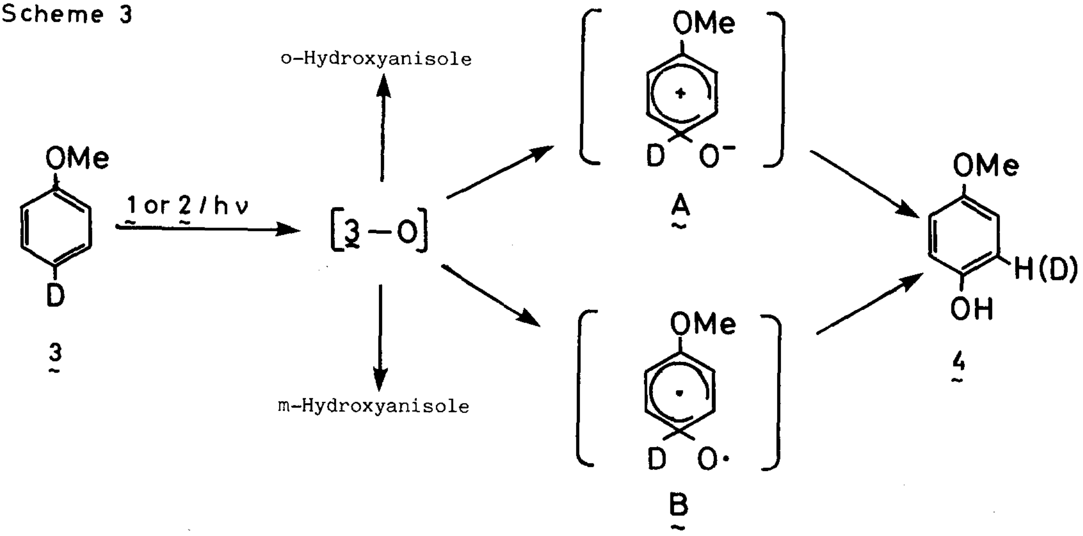


Table 1. Formation Ratios of o-, m-, p-Hydroxyanisole in the Photochemical Hydroxylation of 3 by 1 (o : m : p)

solv. / temp.	Benzene	4-D-Anisole	CH_2Cl_2	Acetone	CH_3CN	MeOH
25 °C	a)	59:10:31	a)	61:12:28	a)	65:5:30
0	a)	68:12:21	a)	68:18:16	a)	65:5:30
-15	60:16:24$^{b)}$	a)	64:11:25	69:17:14	67:16:16	a)
-25	a)	67:16:17	a)	70:15:16	71:13:16	61:8:30

a) Product ratio could not be determined because of occasional overlapping of o-isomer with a rearrangement product on gas chromatograms. b) Solid phase.

Table 2. Deuterium Retntion Values (%) in 4 in the Photochemical Hydroxylation of 3 by 1 or 2$^{a)}$

solv. / temp.	Benzene	4-D-Anisole	CH_2Cl_2	Acetone	CH_3CN	EtOH	MeOH
70 °C	49		34	49	56	75	
25	52	55	35 (38)	42	47 (47)	76	75 (61)
0	48	44	32 (37)	33	30 (42)	78	76
-15	59$^{b)}$		20 (35)	35	28 (39)	80	
-25		39	18	31	27	80	77
-45			15	30	29		74
-78			14	28			

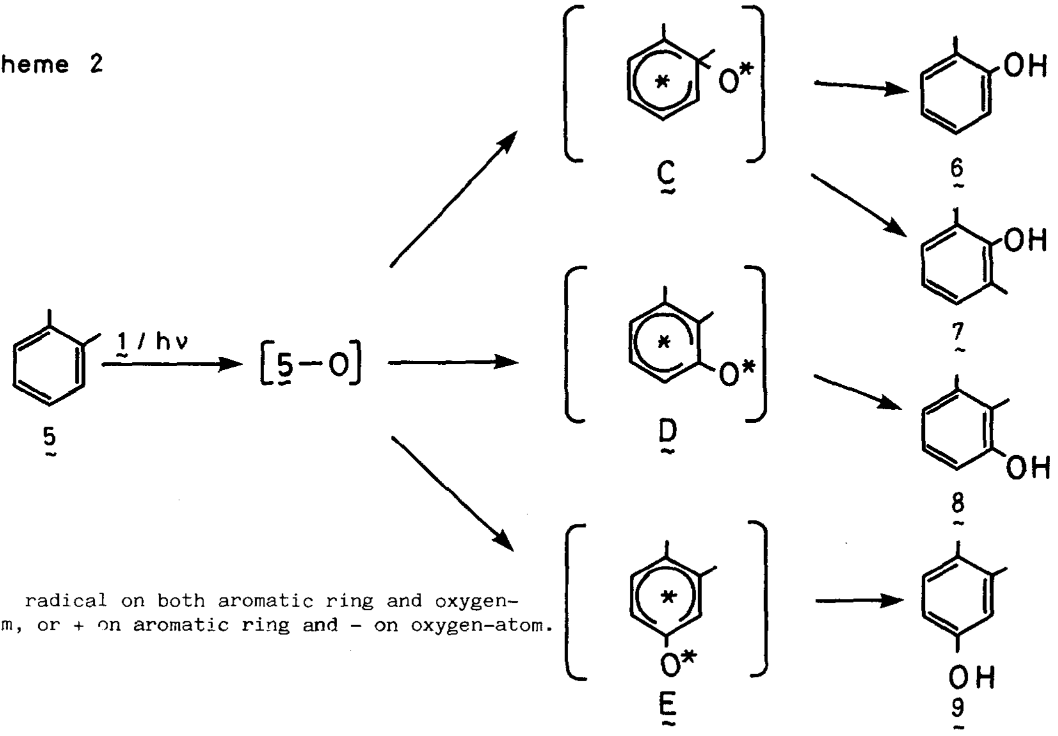
a) The values obtained by 2 are shown in parentheses. b) Solid phase

hydroxylation of 3 (as neat) with $O(^3P)$ atom generated by microwave discharge of $N_2O$$^{5c)}$ (50 % at -35°C and 35 % at 0°C). Temperature effect was observed also on ortho, meta and para ratios (Table 1), although no rational explanation of these phenomena could so far be obtained.

Compound 1 was irradiated also in the presence of o-xylene (5) in three different solvents including 5 itself$^{8)}$, affording the hydroxylation products 6, 7, 8 and 9. Their formation ratios were determined by gas chromatography (5 % Advance-DS, 1.5 m) and are shown in Table 3 together with the results obtained by other methods. The results obtained by photolysis of 1 differed largely from that by microwave discharge of N_2O[5b)] and were found to be similar to that by γ-radiolysis of liquid CO_2[6b)]. These data again show enhancement of the ratios of 1,2 shift vs demethylation (7/6) in polar solvents.

Since photooxygenation of the olefin 10 with 1 in the solvents listed in Table 1 resulted in the formation of 11a, 11b, a mixture of 12a and 12b, and 13 always in almost same ratios (ca 1 : 0.93 : 0.47 : 0.60), the same kind of reactive oxygen species should be generated in all the solvents examined. Therefore the solvent effect observed should be concerned with the structures of the intermediates after addition of oxygen-atom to the aromatic rings. It would be quite conceivable that polar solvents stabilize the dipolar structures such as A (scheme 1) and C (scheme 2, * = + on aromatic ring and - on oxygen-atom) which can be formed by resonance of diradical intermediates as well as by ring opening of arene oxide intermediates, and, consequently, that such dipolar structures probably promote deuteride and methyl shifts. This

Scheme 2

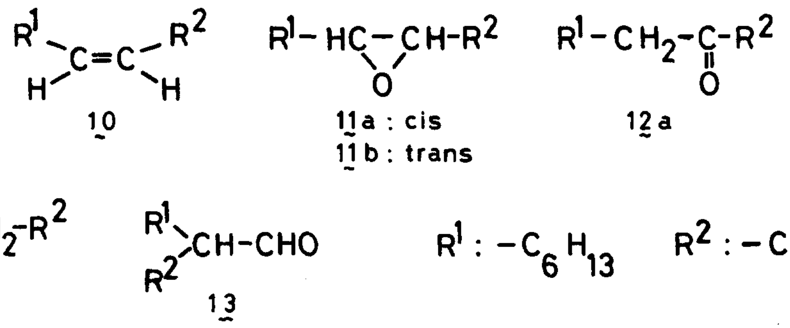


* = radical on both aromatic ring and oxygen-atom, or + on aromatic ring and - on oxygen-atom.

Table 3. Product Ratios in the Photolysis of 1 in the Presence of o-Xylene 5

prod. \ cond.	Microwave discharge of N_2O/-25 °C in o-Xylene[5b)]	γ-Radiolysis of liquid CO_2/0 °C[6b)]	Photolysis of 1/-25 °C o-Xylene	Photolysis of 1/-25 °C CH_2Cl_2	Photolysis of 1/-25 °C MeOH
6	62	—	4	3	2
7	2	7	8	9	16
8	23	37	40	39	39
9	13	55	48	49	44

Scheme 3



R^1 : $-C_6H_{13}$ R^2 : $-C_{10}H_{21}$

argument is consistent with a stepwise dipolar mechanism proposed for NIH-shift(11), and with a suggestion of an alternative route to the arene oxide pathway in phenol formation by hepatic monooxygenases(12)

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7. 4-^{2}H-Anisole (3, d_1 99 %) was prepared by a treatment of 4-Br-Anisole with n-Butyl Lithium to give 4-Lithioanisole followed by its decomposition with D_2O.

8. Photolyses were conducted with 450 W high pressure mercury lamp (UM-452, Ushio Electric Inc.) using a pyrex immersion well (4 - 6 min. irradiation). 0.01 M solution of 3 or 5 containing three equivalent amount of the N-oxide (1 or 2) was taken in a quartz tube (5 mm diameter) and the tube was settled at a fixed position in a quartz Dewar vessel which was filled with cooling agents or water. Photolysis under the same condition was repeated several times to gain reproducible values.

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