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Hydrogen Exchange Reaction of Aminobenzoic Acid. II. Platinum catalyzed Hydrogen Exchange Reaction

Mitsuyoshi Matsuo,[1] Toshiyasu Matsuo,[1a] Takashi Deguchi,[1b] and Yosihiko Kasida[1]

National Institute of Radiological Sciences[1]

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Platinum catalyzed hydrogen exchange reaction of *ortho*, *meta*, and *para* aminobenzoate with deuterium oxide was studied. Deuterium analysis was carried out by nuclear magnetic resonance (NMR) spectrometry and the NMR spectra of aminobenzoic acids and their derivatives were examined to be assigned. All the ring protons of the aminobenzoates exchanged except those *ortho* to the carboxylate ion. It was observed that there were *ortho* activation to amino group and *ortho* deactivation to carboxyl group in the exchange reaction.

Hydrogen exchange reaction with deuterium oxide or tritium oxide in the presence of a platinum catalyst is an important method for introducing the isotope of hydrogen into aromatic compounds. A number of investigations on the platinum catalyzed hydrogen exchange of aromatic compounds have been done.[2-4] Effect of substituents has been studied on the platinum or nickel catalyzed hydrogen exchange reaction of some aromatic compounds.[2,3] However, isotope orientation in disubstituted aromatic compound has been elucidated incompletely.

Table I. The Hydrogen Exchange of Free ABAs in D_2O without Catalyst[a]

Position of proton / Compound	% Approach to statistical equilibrium[b]				
	2	3	4	5	6
o-ABA	—	69	0	84	0
m-ABA	90	—	51	0	74
p-ABA	0	34	—	34	0

a) Each ABA (100 mg) and D_2O (2 ml) were heated at 120° for 10 hr in a sealed tube.
b) statistical equilibrium for each proton: 98.0% deuteration

In the present paper, the isotope orientation of sodium *ortho*, *meta*, and *para* aminobenzoate (Na *o*-, *m*-, and *p*-ABA) in the platinum catalyzed hydrogen exchange reaction has been examined to be compared with that in the acid catalyzed hydrogen exchange reaction of aminobenzoic acids (ABAs) described in the previous paper.[5] Ring protons of free ABAs *ortho* and *para* to amino group exchanged in hot acidic solution[5] and it was anticipated that the acidity of free ABAs themselves would function in the aqueous solution as the acid catalyst of the hydrogen exchange. So Na ABAs were employed to remove the influence of their acidity from our data. As a matter of fact, the ring protons of free ABAs

1) Location: *9-1, 4-Chome, Anagawa, Chiba-shi, Chiba*; *a*) *On leave from Morishita Pharmaceutical Company, Ltd.*; *b*) *On leave from Kyowa Hakko Kogyo Company Ltd.*

2) G.E. Calf, J.L. Garnett, and W.A. Sollich-Baumgartner, "Advances in Tracer Methodology," Vol. 4 (1968); S. Rothchild ed., Plenum Press, New York, U.S.A., 1968, p. 11.
3) R.R. Fraser and R.N. Renaud, *J. Am. Chem. Soc.*, **88**, 4365 (1966).
4) E.A. Evans, "Tritium and its Compounds," Butterworth & Company, Ltd., London, U.K., 1966, p. 127.
5) M. Matsuo, T. Matsuo, Y. Kasida and T. Kondo, *Chem. Pharm. Bull.* (Tokyo), **17**, 495 (1969).

and no hydrogen exchange occurred on the ring protons of Na ABAs under the same condition.

Deuterium analysis of the deuterated ABAs has been carried out by nuclear magnetic resonance (NMR) spectrometry. All the NMR signals of *o*- and *p*-ABA were observed without overlapping and assigned with ease. The specific peaks of the ring protons of *m*-ABA were analyzed as N-acetyl *m*-ABA since the NMR peaks of *m*-ABA were too overlapped to be assigned. The NMR data of ABAs and their derivatives are shown in Table II.

TABLE II. The NMR Spectral Data of ABAs and Their Derivatives

Position of proton / Compound	Chemical shifts (δ)					Coupling constants (Hz)	
	2	3	4	5	6	J_{ortho}	J_{meta}
o-ABA	—	6.75(d)[a]	7.22(t)	6.50(t)	7.71(d)	8.0	1.0 & 2.0
N-Acetyl[b] *o*-ABA	—	8.48(d)	7.43(t)	7.05(t)	8.01(d)	8.0	1.4 & 2.0
3,5-Dichloro *o*-ABA	—	—	7.59(d)	—	7.69(d)	—	2.5
m-ABA	*[c]	—	6.79(m)	*	*	*	*
N-Acetyl[d] *m*-ABA	8.25(s)	—	7.84(d)	7.41(t)	7.64(d)	8.0	1.5
4-Bromo *m*-ABA	7.39(d)	—	—	7.41(d)	7.03(q)	8.4	1.7
p-ABA[e]	7.64(d)	6.58(d)	—	6.58(d)	7.64(d)	8.3	—
N-Acetyl *p*-ABA	7.90(d)	7.72(d)	—	7.72(d)	7.90(d)	8.6	—
3,5-Dibromo *p*-ABA	7.91(s)	—	—	—	7.91(s)	—	—

a) s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet
b) chemical shift of acetyl proton; 2.11 (s)
c) undetermined
d) chemical shift of acetyl proton; 2.09 (s)
e) chemical shift of acetyl proton; 2.11 (s)

o-ABA: The NMR spectrum of *o*-ABA showed two doublets at 6.75 (δ value) and 7.71 and two triplets at 6.50 and 7.22 with small *meta* coupling, each of them corresponding to one proton. The measurement of the *meta* coupling constants revealed that the doublet at 6.75 was coupled with the triplet at 6.50 (J_{meta}=1.0 Hz) and another doublet at 7.71 with another triplet at 7.22 (J_{meta}=2.0 Hz). It was expected that aromatic protons *ortho* and *para* to amino group might be more shielded by its electron releasing effect than the others.[6] On the basis of these observations, the doublet at 6.75 was assigned to H-3, the triplet at 7.22 to H-4, another triplet at 6.50 to H-5 and the remaining doublet at 7.71 to H-6. This assignment was confirmed by the fact that after chlorination of deuterated *o*-ABA, in the spectrum of which only two peaks at 7.22 and 7.71 were found, the 3,5-dichloro derivative obtained gave the same spectrum as 3,5-dichloro ABA; that is, the peaks at 7.22 and 7.71 were due to H-4 and H-6 respectively.

m-ABA: The assignment of the NMR signals of *m*-ABA was difficult because of overlapping. However, the complete separation of the coincident peaks of *m*-ABA was obtained in the spectrum of N-acetyl *m*-ABA, showing a singlet at 8.25, two doublet at 7.64 and 7.84 and a triplet at 7.41. It was suggested from the splitting pattern that a singlet at 8.25 with small *meta* coupling was assigned to H-2 and a triplet at 7.41 to H-5. To assign the remaining doublets the spectra of N-acetyl *m*-ABA, N-acetyl deutero *m*-ABA, 4-bromo *m*-ABA and 4-bromo deutero *m*-ABA were taken. After deuteration by heating in 4N DCl, an aliquot of the deuterated *m*-ABA was acetylated by an ordinary method and the other aliquot was brominated to give 4-bromo deutero *m*-ABA. In the spectrum of N-acetyl deutero *m*-ABA, two peaks of N-acetyl *m*-ABA at 7.64 and 8.25 (H-2) disappeared and the other two peaks at 7.41 (H-5) and 7.84 still remained. On the other hand, the spectrum of *ortho* and *para* to amino group were substitutedi n hot deuterium oxide as shown in Table I

6) H. Spiesecke and W.G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961).

4-bromo *m*-ABA exhibited three signals, a doublet at 7.39 being assigned to H-2, another doublet at 7.41 to H-5 and a quartet at 7.03 to H-6 in considering these coupling pattern, and 4-bromo deutero *m*-ABA gave only a singlet at 7.41 (H-5). This showed that two protons of H-2 and H-6 in *m*-ABA had been substituted by deuterium because the spectrum of 4-bromo deutero *m*-ABA did not show the signal due to H-2 and H-6. Therefore, a peak of N-acetyl *m*-ABA at 7.64 lost in the spectrum of N-acetyl deutero *m*-ABA should be assigned to H-6 and also the remaining signal at 7.84 to H-4.

p-ABA: *p*-ABA gave rise to two doublets at 6.58 and 7.64. The former was assigned to H-3 & -5 and the latter to H-2 & -6 regarding to the shielding effect of amino group mentioned above. This assignment was supported by the finding that bromination of a deutero *p*-ABA showing only a singlet at 7.64 gave 3,5-dibromo derivative, whose spectrum was consistent with that of 3,5-dibromo *p*-ABA.

In view of the lack on any quantitative data, we have determined the deuterium distribution in aromatic ring of Na ABAs on the platinum catalyzed hydrogen exchange reaction with deuterium oxide. Each Na ABA was heated with deuterium oxide in the presence of a prereduced platinum catalyst prepared by the slightly modified Garnett's method.[7] The results of the time course experiments of the exchange reaction are given in Table III.

Table III. The Platinum catalyzed Hydrogen Exchange Reaction of Na ABAs[a]

Position of proton / Reaction time (hr)	% Approach to statistical equllibrium[b]									
	Na *o*-ABA				Na *m*-ABA				Na-*p*-ABA	
	3	4	5	6	2	4	5	6	2 & 6	3 & 5
1	50	38	17	0	0	64	32	0	0	72
5	67	61	31	0	0	100	58	0	0	100
10	100	100	100	0	0	100	100	0	0	100

a) reaction temperature: 120°
b) statistical equilibrium for each proton; 96.3% deuteration

Under these conditions, all the ring protons of Na ABAs except those *ortho* to the carboxylate ion were substituted by deuterium. Garnett, Law and Till have referred to a private communication from Leitch that catalytic exchange involving Na *o*-ABA with deuterium oxide and prereduced platinum oxide at 135° yielded a labeled product in which all ring protons had exchanged except that *ortho* to the carboxylate ion.[8] Leitch's result was in good agreement with ours of Na *o*-ABA.

In the catalytic exchange, amino group seemed to activate *ortho* hydrogen since the most reactive site was the *ortho* position to amino group in each ABA except H-2 of *m*-ABA under the influence of the carboxylate ion. The similar effect has been reported as *ortho* activation of aniline and α-activation of pyridine and quinoline.[2,9,10] Garnett suggested that a charge transfer interaction involving the lone pair of the nitrogen might occur in addition to the formation of the ordinary aromatic π-complex between the substrate and the catalyst, and that the hydrogen exchange might take place by the dissociative π-complex substitution mechanism.[1] The ionized carboxyl group inhibited the exchange of *ortho* hydrogen in Na ABA. For example, the exchange of H-2 of *m*-ABA was difficult although the H-2 would be activated by amino group. The reactivity of the H-2 in the hydrogen exchange was somewhat similar to that in bromination of a typical electrophilic substitution. The bromination

7) J.L. Garnett and W.A. Sollich, *J. Catalysis*, **2**, 339 (1967).
8) J.L. Garnett, S.W. Law and A.R. Till, *Aust. J. Chem.*, **18**, 297 (1965).
9) W.M. Lauer and L.A. Errede, *J. Am. Chem. Soc.*, **76**, 5162 (1954).
10) C.G. Macdonald and J.S. Shannon, *Tetrahedron Letters*, **1964**, 3351.

of H-2 of *m*-ABA retarded for bulkiness of the reaction species (Br^+).[5] In contrast, the H-2 was very reactive in the acid catalyzed exchange which took place by electrophilic attack of deuteron (D^+ or D_3O^+).[5] Therefore, the *ortho* inhibition of the carboxyl group in platinum catalyzed exchange would be caused from steric interaction between the carboxylate ion and the platinum catalyst. Hitherto, it has been reported that there was *ortho* deactivation effect in the exchange reaction of alkylbenzene and monohalogenated benzene because of steric hindrance[2,3] and that *ortho* hydrogen of sodium benzoate was deactivated to some extent.[11] When compared with the acid catalyzed reaction, another remarkable feature of the platinum catalyzed reaction was that ring protons being unaffected by amino and carboxyl group exchanged such as H-4 of *o*-ABA and H-5 of *m*-ABA.

Experimental

Materials——Na *o*-, *m*- and *p*-ABA were prepared from *o*-, *m*- and *p*-ABA to be commercially available. N-Acetyl ABAs were derived from each ABA by an ordinary acetylation, in which no hydrogen exchange occurred. Halogenated and deutero ABAs were obtained by the methods described in the previous paper.[5] Platinum oxide was purchased from Kojima Chemical Co., Ltd. (Tokyo) and deuterium oxide (99.75%) from E. Merck (Darmstadt). Prereduced platinum oxide was prepared by the slightly modified Garnett's method.[7]

Deuterium Analysis——Deuterated samples were analyzed by Varian HA-100 NMR spectrometer. All spectra were run at 100 MHz in diluted solution, the solvent chosen was dimethyl sulfoxide and tetramethylsilane was used as an internal reference. Deuteration ratio was determined by the comparison of the peak intensity between each ring proton and acetyl proton after acetylation of deuterated ABAs.

Exchange Reaction Procedures——Each Na ABA (50 mg) and deuterium oxide (0.5 ml) in the presence of prereduced platinum oxide (2.5 mg) were heated at 120° in a sealed tube. After removal of the catalyst the reaction mixture was adjusted to pH 3 by the addition of dil. HCl to give the precipitate of ABA, while the reaction mixture was evaporated *in vacuo* and the residue was acetylated with a mixture of acetic anhydride and pyridine.

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11) J.L. Garnett, L.J. Henderson, W.A. Sollich and G.V.D. Tiers, *Tetrahedron Letters*, **1961**, 516.