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ALKYLATION OF AMINOHYDROXY ANION, DISSOCIATED SPECIES OF HYDROXYLAMINE

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Abstract——Aminohydroxy anion (3), dissociated species of hydroxylamine, was demonstrated to be nucleophilic on oxygen atom from INDO calculation, and to give directly O-alkylhydroxylamines.

Recently, the preparation of O-alkylhydroxylamines has aroused interests in the pharmacodynamic or chemotherapeutic fields.[1] Since the direct preparation of O-alkylhydroxylamines has never been achieved, we undertook the alkylation on the oxygen atom of hydroxylamine. The pKa values for the first[2] and the second dissociation[3] of hydroxylamine are reported to be 5.97 and 13.7, respectively. These pKa values suggest that the aminohydroxy anion (3) predominantly exists in strongly basic conditions, while free hydroxylamine (2) exists in neutral or weakly basic conditions. By INDO calculation, the HOMO population gave the prediction that the nucleophilic center of 3 was located on oxygen atom and that of 2 was on nitrogen atom.

Table 1

HOMO Population of Hydroxylamine Species, 1, 2 and 3

		NH_3OH^+ (1)	NH_2OH (2)	NH_2O^- (3)
HOMO Population	Nitrogen	0.0885	0.6051	0.2817
	Oxygen	0.7581	0.2262	0.5675

Actually, benzyl bromide (4a) was added to the mixture of hydroxylamine hydrochloride and potassium t-butoxide in t-butanol, and the mixture was allowed to stand at room temperature for 80 min. The reaction products were found to be O-benzyl- (5a), N-benzyl- (6a) and N,N-dibenzylhydroxylamine (7a), which were

identified with the authentic samples. When the product distribution was observed in the change of the rate between potassium t-butoxide and hydroxylamine hydrochloride, 5a increased with the increase of the ratio of t-BuOK/$NH_2OH \cdot HCl$. In using more than 2 molar amounts of potassium t-butoxide, the distribution of 5a was over 60%. From this result, the nucleophilic center of 3 was proved to be mainly on the oxygen atom. Further 5a was directly prepared by the benzylation of 3 optimally using 10 molar amounts of hydroxylamine hydrochloride in the presence of 20 molar amounts of potassium t-butoxide at room temperature for 80 min. Similarly the direct O-alkylation of hydroxylamine was carried out using various alkyl halide.

In conclusion, the nucleophilicity of the aminohydroxy anion (3), a dissociated species of hydroxylamine, was considered to take precedence on oxygen atom. By the use of this property, the direct alkylation, which was convenient and much applicable for the preparation of O-alkylhydroxylamine, was accomplished on the oxygen atom of hydroxylamine.

$$\text{R-X (4)} + \text{NH}_2\text{O}^- \text{ (3)} \longrightarrow \text{R-ONH}_2 \text{ (5)} + \text{R-NHOH (6)} + \text{R}_2\text{NOH (7)}$$

Table 2

Yields and Product Distributions of Alkylation of 3

R-X	Total Yield	Product Distribution		
		5	6	7
$PhCH_2Br$ (4a)	52	66	22	12
$p\text{-}MeC_6H_4CH_2Cl$ (4b)	45	52	13	35
$p\text{-}MeC_6H_4CH_2Br$ (4c)	62	54	24	22
$p\text{-}BrC_6H_4CH_2Br$ (4d)	62	67	19	14
$m\text{-}BrC_6H_4CH_2Br$ (4e)	67	61	25	14
$p\text{-}O_2NC_6H_4CH_2Br$ (4f)*	25	75	18	7
2-Ethylhexyl-Br (4g)**	30	79	21	0

* Sodium methoxide was used as a base in methanol. ** Refluxed for 3 hr.

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