Theoretical and Experimental Aspects of Bromination of Sampangine

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Based on MO calculations and experimental data, the unusual regioselectivity in bromination of sampangine (**1**) is discussed; the proposed mechanism includes initial interaction of bromine or some solvents with nitrogen atom (N-6 in **1**) having a higher electron density.

In the course of structure-activity relationship studies on sampangine (7*H*-naphtho[1,2,3-*i*,*j*][2,7]naphthyridin-7-one) (**1**), a natural prototype of new antifungal agents,[1] we found a peculiar regioselectivity in bromination of **1**. In typical conditions 4-bromosampangine (**3**) was formed exclusively, while in nitrobenzene 3-bromosampangine (**2**) was also obtained.[1b] Although there are numerous publications for halogenation of heterocycles,[2] only a few papers have attempted to explain regioselectivity in mechanistic terms.[3-6]

This paper describes a thorough study of bromination of sampangine with emphasis on both, theoretical and experimental aspects of its unusual selectivity.

We studied the reaction of sampangine with bromine in protic and aprotic solvents of different polarities (Table 1).[7] 4-Bromosampangine (**3**) was exclusively formed in acetic acid or ethanol. On the other hand, the use of some solvents such as acetonitrile, benzonitrile or nitrobenzene changed the regioselectivity of the reaction leading to the formation of increasing amounts of 3-bromosampangine (**2**).

Table 1. Bromination of sampangine (**1**) with Br_2 (2h)

Br_2 eq.	Solvent	Temp. /°C	Conv. /%[a]	Yield /%[b] 2	3	Ratio 2:3
1.2	AcOH	80	82	-	14	-
7	AcOH	80	91	trace	47	-
1.2	EtOH	80	52	-	12	-
7	CCl_4	77	0	-	-	-
7	PhCl	120	71	4	22	15:85
7	PhBr	120	67	2	23	8:92
7	MeCN	80	93	2	25	7:93
7	PhCN	60	43	11	2	85:15
7	PhCN	80	99	30	39	43:57
7	PhCN	100	100[c]	10	39	20:80
7	$PhNO_2$	60	42	22	trace	-
7	$PhNO_2$	80	57	33	0.4	99:1
7	$PhNO_2$	100	75[c]	26	6	81:19

[a]Based on recovered sampangine. [b]Isolated yields of **2** and **3**. The other products consist of a very polar material. [c]3,4-Dibromosampangine was also formed as by-product.

Usually the densities of the highest occupied molecular orbital (HOMO) provide a good predictor of regioselectivity in electrophilic bromination of heterocyclic systems.[8,9] The HOMO densities calculated for sampangine[10] pointed out that the position C-3 was preferential for electrophilic attack. Also the potential energies calculated for the intermediate σ-complexes showed lower values for the 3-bromo intermediate (**2a**) as compared to the 4-bromocounterpart (**3a**) (see Figure 1).[11] However, no reaction at the C-3 was observed under the typical conditions.

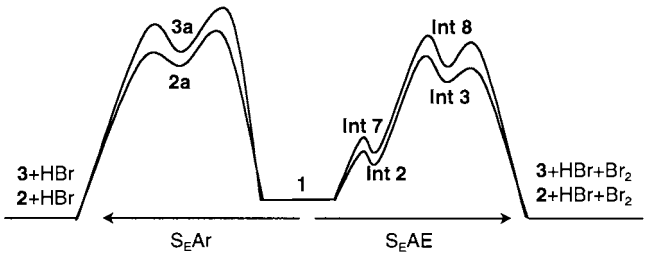
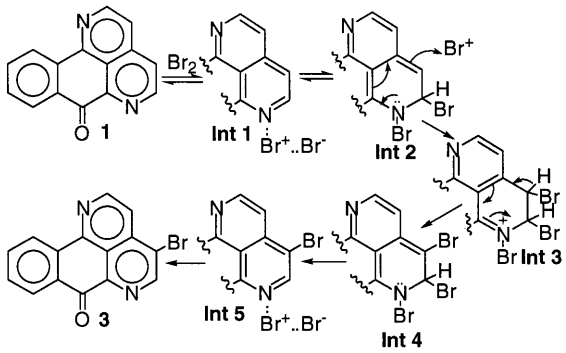


Figure 1. Energy diagram of bromination of sampangine (**1**) in direct substitution mechanism S_EAr (left part) and in proposed mechanism involved initial 1,2-addition-elimination of bromine S_EAE (right part). Potential energy of intermediates in relation to sampangine (**1**) [kcal mol^{-1}]: **2a**:142.6; **3a**:154.7; **Int 2**:46.2; **Int 3**:133.1; **Int 7**:46.8; **Int 8**:140.9; **2**:-4.3; **3**: -4.2 (approximate scale). Formation of the complex between sampangine and nitrobenzene lowers energy of the corresponding intermediates by 5-5.7 kcal mol^{-1}

This situation prompted us to assume that the bromination of sampangine does not go through the direct electrophilic substitution, but rather through the addition-elimination mechanism presented in Scheme 1.



Scheme 1. Proposed mechanism for C-4 bromination of **1**.

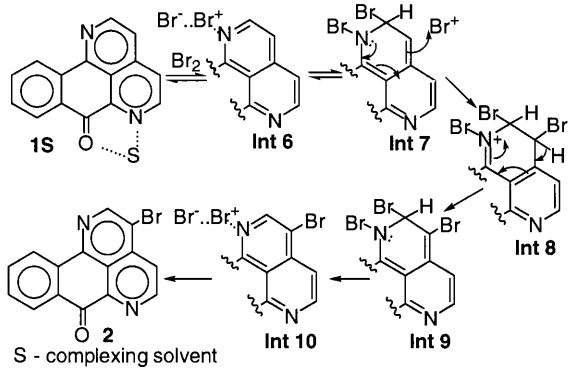
In this mechanism a bromine atom forms an initial intermediate adduct (**Int 1**) with nitrogen atom N-6 of sampangine, followed by reversible 1,2-addition of bromine to C=N bond of pyridine ring (**Int 2**). The next step is an irreversible addition of

bromine ion to form the intermediate **Int 3**. From that point a substitution of hydrogen atom takes place with eventual formation of 4-bromosampangine (**3**). The minimum energies of intermediates calculated for **Int 2** and **Int 3** have now lower values than the intermediate in direct substitution (**2a**) and the corresponding counterparts (**Int 7** and **Int 8**) for bromination at the position C-3. This supports the preferential bromination at the sampangine C-4 position under the typical conditions.

This plausible mechanism assumes the higher electron density of nitrogen atom N-6 in sampangine. This assumption is in conflict with the currently accepted generalization that pyridines containing electron-withdrawing groups such as carbonyl at the α-position are weaker bases. This generalization, however, has been found to be not valid for a rigid sampangine system with *s-cis* configuration of carbonyl group and nitrogen atom N-6. The proximity of a lone pair of electrons of N-6 and carbonyl oxygen in such a system should result in interaction between these lone pair orbitals. *Ab initio* calculations (HF/6-31G* level) clearly indicate the presence of such interaction.[12] The orbitals on N-6 are distorted[13] and the lone pair of electrons has a higher energy than those on N-1. The charge calculations based on fit to the electrostatic potential (ESP method) suggest that N-6 has higher electron density.[14] Also ^{15}N-NMR experiments with sampangine show that nitrogen atom at position N-6 is protonated first.[15] Only the corresponding Mulliken charges showed opposite result.[1c] This contradiction may be related to the properties of this method which, being the simplest partitioning scheme, may not adequately consider the variation of the charge population based on the interaction of the lone pair orbitals.

The change in the regioselectivity of bromination in acetonitrile, benzonitrile, or nitrobenzene can be explained now on the basis of the formation of complexes (e.g.**1S**) between those solvents and nitrogen atom N-6 and/or carbonyl oxygen that hinders N-6 from forming an initial adduct (**Int 1**) with bromine.[16] In such circumstances, bromine may form an adduct (**Int 6**) with an available nitrogen atom N-1, leading to the formation of 3-bromosampangine (**2**) in similar chain of events, like in the case of 4-bromination (see Scheme 2).

The largest amounts of **2** were formed in nitrobenzene, which must make the most stable complex with sampangine.[17] A decrease in the yield of **2** with an increase of the temperature can be ascribed to a decrease in the association constant of charge-transfer complexes.[18]



Scheme 2. Proposed mechanism for C-3 bromination of **1**.

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Supporting Information (7 pages) including spectral and molecular orbital calculation data are available on request to the authors by FAX (662-915-7026).

Reference and Notes

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7. Each **2**/**3** ratio in Table 1 reflects only regioselectivity in the formation of these products. The relatively low yields of **2** and **3** might be caused by concomitant side reactions arising from hydrogen bromide liberated in the reaction.
8 M. R. Grimmett, *Adv. Heterocycl. Chem*., **47**, 393 (1990), and references cited therein.
9 R. W. Weber, S. -J. Lee, S. Milosevich, W. B. England, and J. M. Cook, *Can. J. Chem*., **60**, 3049 (1982).
10 The HOMO values showing m/e 0.0175 eV at C-3 and 0.0123 eV at C-4, were calculated using the HOMO map by AM1 method.
11 All computational calculations were performed with the SPARTAN V 5.0 program (Wavefunction Inc., CA) mounted on the Indigo^2 Worksation (Silicon Graphics, Inc. CA). All geometries were optimized at the AM1, and energies were calculated using these geometries at the HF/3-21G(*) (unless otherwise noted).
12 The overlap between the same orbital phase gives higher energy orbital (HOMO-4) and that of opposite phase gives lower energy orbital (HOMO-7) in contrast to the generalization of MO theory. This contradiction may be ascribed to the localization of electrons in the significantly distorted orbital (HOMO-4), which seems to be formed from incomplete agreement of symmetry between lone pair orbitals of N-6 and carbonyl oxygen in sampangine.
13 *Ab initio* calculations (HF/6-31G* level) suggest the presence of deviation of angle (approximately 5-10˚), based on the distortion from the usual direction of electrophilic attack on nitrogen atom in pyridines.
14 The ESP charges on nitrogen atoms N-1 and N-6 were calculated as - 0.70 and - 0.71 (MNDO), - 0.64 and - 0.67 (AM1), and - 0.64 and - 0.68 (PM3) correspondingly.
15 Site of protonation was found by running ^{15}N-NMR titration of sampangine with sulfuric acid in DMSO-d_6.
16 Charge transfer complexes between azines and aromatic nitrocompounds were observed before, see R. M. Issa, N. T. Abdel-Ghani, A. L. El-Ansary, and A. F. Shoukry, *Rev. Roum. Chim.*, **26**, 667 (1981).
17 The ^{15}N-NMR data support a possible formation of the complex; the signal of N-6 in nitrobenzene appears at a significantly lower field than that in chloroform and DMSO. The chemical shifts (ppm, referred to nitromethane) of N-6 are 320.2 (in $CDCl_3$), 324.9 (in DMSO-d_6) and 349.6 (in $C_6D_5NO_2$) respectively.
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