

Superactivity and Dual Reactivity of the System *N*-Iodosuccinimide–H₂SO₄ in the Iodination of Deactivated Arenes

V. K. Chaikovskii^a, V. D. Filimonov^a, V. I. Skorokhodov^a, and V. D. Ogorodnikov^b

^a Tomsk Polytechnic University, pr. Lenina 30, Tomsk, 634050 Russia
e-mail: clg@mail.ru

^b Institute of Petroleum Chemistry, Siberian Division, Russian Academy of Sciences, Tomsk, Russia

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Abstract—Dissolution of *N*-iodosuccinimide in sulfuric acid gives rise to electrophilic iodine-containing species which are capable of successfully iodinating aromatic compounds with electron-withdrawing substituents in the temperature range from 0 to 20°C. The iodination in sulfuric acid is effected by both protonated *N*-iodosuccinimide and IOS(O)(OH⁺)OH intermediate.

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We previously found that superactive electrophilic iodine capable of readily iodinating at 0°C strongly deactivated arenes is formed in sulfuric acid from iodine chloride and silver sulfate [1, 2] or from 2,4,6,8-tetraiodoglycoluril (1,3,4,6-tetraiodooctahydroimidazo-[4,5-*d*]imidazole-2,5-dione) [3]. *N*-Iodosuccinimide (NIS) has long been regarded as a weak iodinating agent [4, 5] until Olah et al. [6, 7] have shown that NIS in high-cost trifluoromethanesulfonic acid or in BF₃–H₂O is capable of nitrating nitrobenzene and some other deactivated arenes. Our preliminary results showed that in the iodination of nitrobenzene expensive trifluoromethanesulfonic acid can be successfully replaced by accessible sulfuric acid [8]. The same system (NIS–H₂SO₄) was used to effect selective iodination of 4-chloro-2-nitrotoluene [9].

The goal of the present work was to study in detail preparative potential of the reagent obtained by dissolution of NIS in H₂SO₄ using deactivated aromatic compounds as substrates and determine the nature of electrophilic iodine-containing species generated in that medium. Dissolution of NIS in 90% sulfuric acid (*d* = 1.814 g/cm³) gave a stable dark brown solution which exhibited enhanced iodinating power. It readily reacted with many deactivated aromatic compounds at 0°C or at room temperature to give the corresponding iodo-substituted derivatives (Table 1). Carbonyl compounds, such as benzaldehyde (**Ia**), benzophenone (**IIa**), and benzil (**IIIa**) were converted in 30 min at

0°C into 3-iodobenzaldehyde (**Ib**), 3,3'-diiodobenzophenone (**IIb**), and 3,3'-diiodobenzil (**IIIb**), respectively. The syntheses of 2,7-diiodofluorenone (**IVb**) and 2,7-diiodophenanthrenequinone (**Vb**) from fluorenone (**IVa**) and phenanthrenequinone (**Va**) were accompanied by tarring, but the complete transformation of the initial compounds also required 30 min at 0°C. The iodination of benzoic (**VIa**) and 4-fluorobenzoic acids (**VIIa**) was slower than the iodination of aldehydes and ketones. The reason is not clear, but analogous reduced reactivity of aromatic carboxylic acids was observed by us previously in the iodination with iodine(I) chloride in sulfuric acid [10].

The results of iodination strongly depend not only on the electronic structure but also on the solubility of substrates and other factors. For example, we failed to selectively introduce one iodine atom into iodobenzene (**VIIIa**) molecule or obtain hexaiodobenzene under the given conditions. The iodination of **VIIIa** with a solution of 2 or 4 equiv of NIS in H₂SO₄ gave a complex mixture of mono-, di-, tri-, and tetraiodobenzenes (according to the GC–MS data). However, in the iodination of **VIIIa** with 10 equiv of NIS 1,2,4,5-tetraiodobenzene (**VIIIb**) was formed in 68% yield (Table 1). No further iodination occurred, for tetraiodobenzene **VIIIb** is almost insoluble in sulfuric acid (it completely separates from the solution once being formed).

4-Nitrotoluene (**IXa**) is poorly soluble in sulfuric acid; therefore, only the dissolved part of substrate **IXa**

Table 1. Iodination of deactivated aromatic compounds with *N*-iodosuccinimide in sulfuric acid

Substrate (no.)	Temperature, °C	Reaction time, min	Product	Yield, %	mp, °C (solvent); published data
Benzaldehyde (Ia)	0	30	3-Iodobenzaldehyde (Ib)	80	54–56 (EtOH); 57 [14]
Benzophenone (IIa)	0	30	Bis(3-iodophenyl)methanone (IIb)	63	145–147(EtOH); 147–149 [17]
Benzil (IIIa)	0	30	1,2-Bis(3-iodophenyl)ethane-1,2-dione (IIIb)	79	128–129 (EtOH); 128–129 [16]
Fluorenone (IVa)	0	30	2,7-Diiodofluorenone (IVb)	35	205–206 (benzene); 205–206 [14]
Phenanthrenequinone (Va)	0	30	2,7-Diiodophenanthrenequinone (Vb)	20	309–310 (toluene); 310 [14]
Benzoic acid (VIa)	0	120	3-Iodobenzoic acid (VIb)	42	185–186 (50% <i>i</i> -PrOH); 186–187 [14]
4-Fluorobenzoic acid (VIIa)	0	120	4-Fluoro-3-iodobenzoic acid (VIIb)	73	173–174 (80% <i>i</i> -PrOH); 174–176 [3]
Iodobenzene (VIIIa)	0	30	1,2,4,5-Tetraiodobenzene (VIIIb)	68	250–253 (DMF); 254 [15]
4-Nitrotoluene (IXa)	0	30	2-Iodo-4-nitrotoluene (IXb)	55	55–57 (EtOH); 58 [14]
	20	80	2,6-Diiodo-4-nitrotoluene (IXc)	68	115–116 (EtOH); 117–118 [2]
2-Nitrotoluene (Xa)	0	60	4-Iodo-2-nitrotoluene (Xb)	41	58–59 (MeOH); 60–61 [14]
Nitrobenzene (XIa)	0	90	3-Iodonitrobenzene (XIb)	77	35–36 (EtOH); 36–37 [8]
	20	20		79	35–36 (EtOH)
	20	1200		78	35–36 (EtOH)

undergoes iodination. As a result, the reaction mixture contains the initial compound and moniodination product, 2-iodo-4-nitrotoluene (**IXb**), at comparable concentrations; further iodination of compound **IXb** gives 1,3-diiodo-2-methyl-5-nitrobenzene (**IXc**), and both mono- and diiodo derivatives and initial nitrotoluene **IXa** are present in solution. Nevertheless, we found that the solubility problem can be partially eliminated by using finely powdered substrate and vigorously stirring the reaction mixture. In such a way we succeeded in obtaining moniodo derivative **IXb** in 55% yield (Table 1). Raising the temperature to 20°C and using a solution of 4 equiv of NIS led to the formation of only diiodo derivative **IXc**.

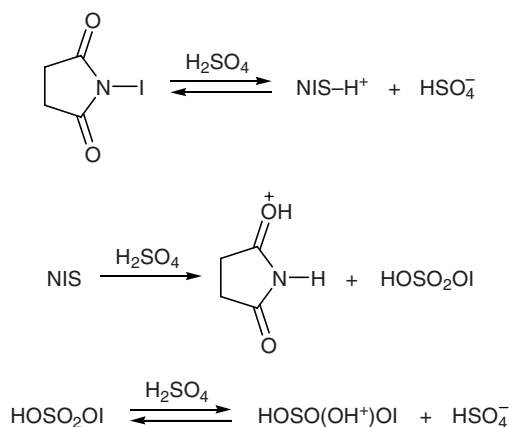
Liquid *o*-nitrotoluene (**Xa**) is better soluble in sulfuric acid, and it is readily iodinated with NIS in H₂SO₄ at 0°C. However, due to high reactivity of the iodinating agent, a mixture of two moniodo derivatives and small amounts of diiodonitrotoluenes is formed (GC–MS data). By recrystallization from ethanol we isolated 41% of 4-iodo-2-nitrotoluene (**Xb**) (Table 1).

While studying iodination of deactivated arenes with NIS–H₂SO₄ we were the first to reveal two types of reactivity of NIS in sulfuric acid. According to the

TLC data, the reaction of nitrobenzene (**XIa**) with an equimolar amount of NIS at 20°C in 20 min resulted in ~50% conversion of **XIa** into 3-iodonitrobenzene (**XIb**), while iodination of the remaining substrate required ~19–20 h. An analogous pattern was observed when the iodination was performed at 0°C. In this case, ~50% conversion of nitrobenzene was attained in 1.5 h, but no transformation of **XIa** into **XIb** occurred during the next 24 h. On the other hand, the iodination of nitrobenzene (**XIa**) with 2 equiv of NIS was complete in 1.5 h at 0°C and in 18–20 min at 20°C.

The ¹³C NMR spectrum of a solution of NIS in H₂SO₄ at 20°C contained two carbonyl carbon signals at δ_C 188.3 and 191.0 ppm with an intensity ratio of 55:45. These signals are displaced by 10.7 and 12.6 ppm downfield relative to the corresponding signals of NIS and succinimide in DMSO-*d*₆. Therefore, the signal at δ_C 188.3 ppm was assigned to protonated succinimide, and that at δ_C 191.0 ppm, to protonated *N*-iodosuccinimide NIS-H⁺. We presumed that NIS quickly loses more than half of iodine upon dissolution in sulfuric acid; however, its complete acidolysis to succinimide does not occur even on storage over two days. These findings may be rationalized as shown in Scheme 1.

Scheme 1.



Presumably, the dual reactivity of NIS in sulfuric acid results from the presence of two types of electrophilic iodinating species, protonated NIS and iodine(I) hydrogen sulfate HOSO_2OI or protonated form of the latter. In order to estimate on a quantitative level the reactivities of NIS and electrophilic iodine-containing intermediates formed according to Scheme 1, we performed their geometry optimization and calculated their standard enthalpies of formation and Gibbs energies in terms of the density functional theory (DFT). The calculations were performed by the B3LYP method [11] with extended 6-311G* basis set (10s9p5d basis set for iodine atom [12]) in the natural bond orbital (NBO) approximation using GAUSSIAN'98W software [13]. The results are given in Table 2. Electron deficiency on the iodine atom (i.e., its electrophilicity) strongly increases in going from NIS (0.273) to the assumed hypoiodite-like intermediate HOSO_2OI (0.376). Polarization of the iodine–heteroatom bond increases in the same order, while the order of that bond decreases.

Protonation of IOSO_2OH and NIS may occur at both heteroatoms directly attached to iodine and double-bonded oxygen atoms of the S=O and C=O

Table 2. Charges on the iodine atom (q_I) and heteroatom attached thereto (q_X), I–X bond lengths, their polarizations, and Wiberg indices in iodine-containing electrophilic species, calculated at the B3LYP/6-311G* NBO level

Iodinating species	q_I	q_X	Bond length, Å	Bond polarization, %	Wiberg index
IOSO_2OH	0.376	−0.575	2.065	73.78	0.742
$\text{IOSO}_2\text{OH}_2^+$	0.590	−0.553	2.119	81.25	0.588
NIS	0.273	−0.598	2.065	69.41	0.797
NIS-H^+	0.444	−0.585	2.080	73.09	0.765

groups. In the latter case, the enthalpies of formation of the monoprotonated structures are lower approximately by 84 kJ/mol than those of alternative structures (an analogous conclusion was recently drawn on the basis of B3LYP/6-311G** quantum-chemical calculations of protonated forms of *N*-chlorosuccinimide [7]). Therefore, the structure $\text{IOS(O)(OH}^+\text{)OH}$ was selected for the protonated form of acyl hypoiodite.

As might be expected, protonation considerably increases the electrophilicity of iodine. Electron deficiency of the iodine atom in the above protonated species changes in the same order as for the corresponding neutral precursors. Protonation leads to extension of the heteroatom–iodine bonds, increases their polarization, and reduces their order as compared to neutral compounds.

The fact that $\text{IOS(O)(OH}^+\text{)OH}$ is a considerably stronger electrophile than NIS-H^+ is very consistent with the observed dual reactivity of NIS in sulfuric acid. According to the calculations, the more active component of the reaction mixture is the product of iodine transfer from *N*-iodosuccinimide to sulfuric acid, $\text{IOS(O)(OH}^+\text{)OH}$. The results of thermochemical calculations for iodine exchange reactions of NIS and NIS-H^+ with sulfuric acid are given in Scheme 2. The low positive values of ΔH and ΔG indicate that iodine transfer to sulfuric acid is thermodynamically feasible; they also conform to the above NMR data which suggest that dissolution of NIS in sulfuric acid gives rise to approximately equimolar amounts of protonated forms of NIS (NIS-H^+) and succinimide.

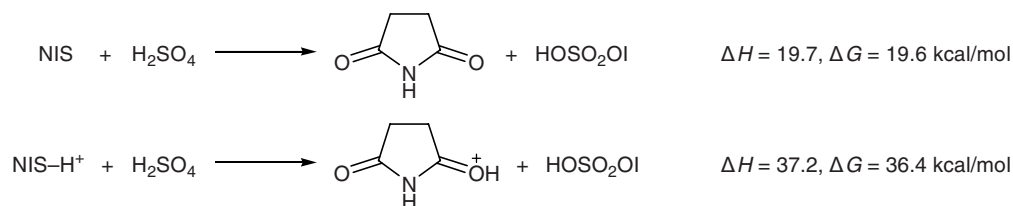
EXPERIMENTAL

The ^{13}C NMR spectra were recorded on a Bruker AC-300 spectrometer. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using benzene (I–V), hexane (VIII), hexane–acetic acid (10:1) (VI, VII), or carbon tetrachloride (IX–XI) as eluent; spots were visualized under UV light.

The iodination products were identified by comparing their spectral and analytical data with those of authentic samples, as well as by measuring melting points of mixed samples (no depression was observed). *N*-Iodosuccinimide was synthesized by the procedure described in [8].

Iodination of deactivated aromatic compounds Ia–XIa with *N*-iodosuccinimide in sulfuric acid (general procedure). Sulfuric acid ($d = 1.814 \text{ g/cm}^3$,

Scheme 2.



90%), 30 ml, was cooled to 0–5°C and added to 2.25 g (10 mmol) of *N*-iodosuccinimide, and the mixture was stirred for 20–30 min until it became homogeneous. To effect monoiodination, 5 mmol of the corresponding arene was added at 0 or 20°C (Table 1) to the resulting dark brown solution, and the mixture was vigorously stirred for 20–180 min. To introduce two iodine atoms into the substrate molecule, its amount was reduced by half. When the reaction was complete, the mixture was poured into 100 ml of an ice–water mixture and treated with a solution of Na₂SO₃. Compounds **Ib**, **Xb**, and **XIb** were extracted into methylene chloride, the extract was dried over CaCl₂, the solvent was distilled off, and the residue was recrystallized if necessary. Compounds **IIb**, **IIIb**, **VIb–VIIIb**, **IXb**, and **IXc** were filtered off, dried, and recrystallized from appropriate solvent (Table 1). Compounds **IVb** and **Vb** were dissolved in benzene, the solution was filtered through a layer of silica gel, and the solvent was distilled off from the filtrate.

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