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Evaluation of the Reactivity and Regioselectivity of Superelectrophilic Iodinating Systems

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Abstract—Iodination of *o*-nitrotoluene in H_2SO_4 or CF_3SO_3H at 0°C with compounds having a nitrogen–iodine bond leads to the formation of isomeric mono- and diiodo derivatives whose ratio differs from the statistical value. The reaction of nitrobenzene with 2 equiv of N–I reagents in trifluoromethanesulfonic acid at 0°C takes less than 1 min and yields 79–85% of *m*-iodonitrobenzene. The electrophilic reactivity of the iodinating agents was estimated by quantum-chemical methods.

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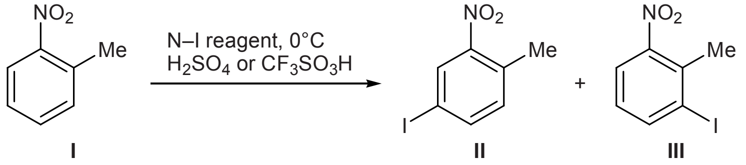
The rate of electrophilic substitution reactions in the aromatic series and isomeric composition of the products are largely determined by the electrophile nature. In keeping with the Brown selectivity relationship, stronger electrophiles exhibit lower intramolecular selectivity in substitution reactions in the benzene ring [1]. The most reactive electrophiles give rise to a mixture of regioisomers whose ratio approaches statistical value. In the iodination with common iodinating systems, the reactivity and selectivity may be evaluated using the reaction with toluene as an example [2]. However, the procedure based on determination of the ratio of *o*- and *p*-iodotoluenes cannot be applied to reactions with superelectrophilic iodinating systems [3–6], which lead to the formation of a mixture of polyiodotoluenes containing mostly tri- and tetraiodo derivatives. Therefore, to estimate the selectivity of superelectrophilic iodinating systems we compared the compositions of products formed in the iodination of *o*-nitrotoluene (**I**) with reagents generated by dissolution of 1,3,4,6-tetraiodoglycoluril (TIG), 1,3-diiodo-5,5-dimethylhydantoin (DIH), and *N*-iodosuccinimide (NIS) in sulfuric acid [3, 5, 6] (Scheme 1).

Traditional methods for the determination of the reactivity and regioselectivity of iodinating systems by analysis of the iodination products of nitroarene **I** cannot be used, for nitrotoluenes do not undergo iodination by common methods at 0°C. Detailed GC–MS study on the products of reactions of compound **I** with TIG–H_2SO_4, DIH–H_2SO_4, and NIS–H_2SO_4 showed (Table 1) that the use of stoichiometric amounts of the reagents (calculated on the active iodine) does not ensure complete conversion of **I** (Table 1, run nos. 1–3), and 30–35% of the initial compound remains unchanged.

A similar conversion of other substrates at the same reagent-to-substrate ratio was noted by us previously [3–6]. Approximately similar selectivities were observed in the iodination with TIG–H_2SO_4 and DIH–H_2SO_4. In the reaction with *N*-iodosuccinimide, the fraction of 4-iodo-2-nitrotoluene (**II**) was slightly larger than the fraction of 6-iodo-2-nitrotoluene (**III**), but the substrate conversion was lower.

The reactions in the presence of 2 equiv of the iodinating agents (Table 1, run nos. 4–6) are characterized by appreciably reduced *para*-selectivity. However,

Scheme 1.



I **II** **III**

Table 1. Iodination of *o*-nitrotoluene (**I**) in sulfuric acid (d = 1.814 g/cm^3) at 0°C

Run no.	Reagent	Molar ratio **I**–reagent	Reaction time, min	Product ratio **II**:**III**, %	Unreacted substrate **I**, %
1	TIG–H_2SO_4	1:0.25	60	14:86	30
2	DIH–H_2SO_4	1:0.5	60	14:86	32
3	NIS–H_2SO_4	1:1	60	12:88	35
4	TIG–H_2SO_4	1:0.5	30	19:81	0
5	DIH–H_2SO_4	1:1	30	23:77	0
6	NIS–H_2SO_4	1:2	30	22:65[a]	0

[a] In addition, five isomeric diiodonitrotoluenes and one triiodonitrotoluene were detected.

Table 2. Iodination of *o*-nitrotoluene (**I**) with the system NIS–H_2SO_4 at 0°C (substrate–reagent ratio 1:2)

Iodination product	Retention time, min	Mass spectrum, m/z (I_{rel}, %)	Fraction, %
6-Iodo-2-nitrotoluene (**III**)	14.54	263 $[M]^+$ (39), 246 (100), 218 (8), 127 (4), 119 (23) 90 (60), 78 (5), 63 (21), 39 (2)	22
4-Iodo-2-nitrotoluene (**II**)	14.74	263 $[M]^+$ (41), 246 (100), 218 (11), 127 (5), 119 (14), 89 (35), 63 (16), 39 (3)	65
4,6-Diiodo-2-nitrotoluene	18.67	389 $[M]^+$ (48), 372 (100), 344 (21), 245 (20), 216 (43), 189 (5), 127 (9), 105 (11), 89 (82), 63 (35), 39 (9)	9.9
Diiodo-2-nitrotoluenes (4 isomers)	18.46	389 $[M]^+$ (100), 372 (81), 343 (4), 245 (71), 216 (68), 189(4), 165 (3), 127 (13), 105 (9), 89 (82), 63 (46), 39 (11)	2.9
	18.89	389 $[M]^+$ (100), 372 (48), 343 (9), 254 (12), 245 (21), 216(60), 127 (17), 118 (21), 89 (86), 63 (50), 50 (11), 39 (8)	
	19.19	389 $[M]^+$ (90), 372 (100), 344 (8), 254 (7), 245 (35), 216(40), 189 (6), 127 (11), 105 (14), 89 (95), 63 (47), 39 (12)	
	19.27	389 $[M]^+$ (76), 372 (100), 343 (10), 245 (39), 216 (44), 189 (4), 127 (9), 105 (10), 89 (74), 63 (35), 39 (8)	
Triiodo-2-nitrotoluene	22.60	515 $[M]^+$ (100), 498 (50), 485 (10), 371 (14), 342 (51), 244 (38), 215 (81), 165 (14), 127 (19), 88 (49), 62 (26), 44(4)	0.2

in the iodination with TIG–H_2SO_4 and DIH–H_2SO_4 only monoiodo derivatives were detected, whereas the system NIS–H_2SO_4 gave rise to a mixture of monoiodination products, five isomeric diiodonitrotoluenes (overall yield ~13%), and traces of triiodonitrotoluene (Table 2). As might be expected, replacement of sulfuric acid by considerably stronger trifluoromethanesulfonic acid resulted in slightly reduced regioselectivity (Table 3). Furthermore, despite the presence of excess iodinating agent (2 equiv), neither di- nor polyiodo derivatives were detected by GC–MS in the reaction mixtures obtained in trifluoromethanesulfonic acid, and even up to 3% of initial *o*-nitrotoluene **I** remained unchanged.

The iodination of **I** was carried out over a period of 15 min; however, it turned out that the process was considerably faster. Initially, we relied upon the data of [7], according to which the iodination of nitrobenzene **IV** and some other deactivated aromatic compounds with *N*-iodosuccinimide in trifluoromethanesulfonic acid was performed at 20°C, and the yield of 3-iodonitrobenzene (**V**) was 86% in 2 h. We tried to reproduce the results reported in [7] and found that the reaction with stoichiometric amounts of the reactants (**IV**:NIS = 1:1) takes less than 1 min even at 0°C, but the substrate conversion is no more than 61–65%. By carrying out the reaction at 20°C for 5 and 20 h we succeeded in attaining no more than 65% conversion of arene **IV** into 3-iodonitrobenzene (**V**) (GC–MS data). However, the use of 2 equiv of NIS, as well as of TIG and DIH, ensured complete conversion of **IV** into iodo derivative **V** in a few seconds, i.e., in this case the process may be regarded as a “test-tube” reaction (Table 4).

Moreover, the reaction took less than 1 min at 0°C, and the yield of **V** ranged from 79 to 85%, depending

Table 3. Iodination of *o*-nitrotoluene (**I**) in trifluoromethanesulfonic acid at 0°C

Run no.	Reagent	Molar ratio **I**–reagent	Reaction time, min	Product ratio **II**:**III**, %	Unreacted substrate **I**, %
1	TIG–CF_3SO_3H	1:0.5	15	25:72	3
2	DIH–CF_3SO_3H	1:1	15	22:76	2
3	NIS–CF_3SO_3H	1:2	15	27:71	2

Table 4. Iodination of nitrobenzene (**IV**) in trifluoromethanesulfonic acid

Reagent	Molar ratio **IV**–reagent	Reaction time	Temperature, °C	Yield of **V**, %
NIS–CF_3SO_3H	1:2	<1 min	20	83[a]
NIS–CF_3SO_3H	1:2	1 min	0	85[a]
NIS–CF_3SO_3H	1:1	1 min	0	61
NIS–CF_3SO_3H	1:1	20 h	20	65
TIG–CF_3SO_3H	1:1	1 min	0	79[a]
DIH–CF_3SO_3H	1:0.5	1 min	0	82[a]

[a] Preparative yield.

on the iodinating agent (Table 4). As far as we know, this is the best result in the iodination of deactivated arenes, in particular of nitrobenzene (**IV**).

We previously showed, first by theoretical methods [8] and then experimentally [9], that disproportionation of hypoiodite $I^+HSO_3^-$ generated upon dissolution of N-iodo reagents (NIS, TIG, and DIH) in sulfuric acid could give rise to $I_3^+HSO_4^-$. Presumably, I_3^+ could also be generated from $I^+CF_3SO_3^-$ which is likely to arise upon dissolution of NIS [7], as well as of TIG and DIH, in CF_3SO_3H. We believe that just I_3^+ $F_3CSO_3^-$ should exhibit the highest electrophilicity in the examined systems. With a view to compare the electrophilities of reactive species that could be involved in the iodination process, the structures of $I^+HSO_3^-$ and $I_3^+HSO_3^-$, as well as of $I^+F_3CSO_3^-$ and $I_3^+F_3CSO_3^-$, were optimized at the NBO RHF/6-311G(*d*) level of theory in the gas phase; Table 5), and their global electrophilicities (ω) [10] were determined.

According to the B3LYP/6-311G(*d*) calculations [8], the I_3^+ cation has a trigonal structure with an I–I–I bond angle of 107.8°. Our calculations gave a value of 103.3° for I_3^+, and the corresponding angles in $I_3^+HSO_4^-$ and $I_3^+CF_3SO_3^-$ were estimated at 96.1 and 96.6°, respectively. These values are typical of multivalent iodine compounds [11] and complexes like $I_3^+AlCl_4^-$ and $I_3^+AsF_6^-$ [12]. The lowest unoccupied molecular orbital in the examined species is localized on the I–I–I fragment; this means that their electrophilicity is related mainly to central iodine atom. The data in Table 5 confirm that hypoiodites derived from the stronger acid exhibit stronger electrophilicity and that species like $I_3^+An^-$ (where An^- is the corresponding acid anion) are considerably more electrophilic than reagents like I^+An^-.

EXPERIMENTAL

The progress of reactions was monitored by thin-layer chromatography using Sorbfil plates and carbon tetrachloride as eluent; spots were visualized under UV light. Initial *o*-nitrotoluene (**I**) and nitrobenzene (**V**) were distilled under reduced pressure and analyzed by GLC. Sulfuric acid of chemically pure grade and trifluoromethanesulfonic acid (from Angarsk Electrolysis

Table 5. Ionization potentials (*IP*), electron affinities (*EA*), global electrophilicities (ω), and charges on the iodine atoms [*q*(I)] in iodinating agents, calculated for the gas phase at the RHF/6-311G(*d*) level using natural bond orbital (NBO) approximation[a]

Iodinating agent	$IP = -E_{\mathrm{HOMO}}$	$EA = -E_{\mathrm{LUMO}}$	*q*(I)	ω, eV
I_3^+	14.930	6.437	0.503	6.720
$IHSO_4$	11.342	0.570	0.482	1.647
$I_3^+HSO_4^-$	10.804	2.416	0.738	2.604
CF_3SO_3I	11.546	0.908	0.507	1.823
$I_3^+CF_3SO_3^-$	11.082	2.489	0.707	2.679

[a] Imaginary frequency 66.4 cm^{-1}.

and Chemical Complex) containing no less than 99.5% of the main substance were used.

Gas chromatographic–mass spectrometric analysis was performed on a Trace DSQ instrument (Thermoelectron Corp.); Xcalibur 1.4 software; BPX5 capillary column, 25 m; injector temperature 280°C; oven temperature programming from 70 to 250°C at a rate of 15 deg/min; a.m.u. range 33–500. Quantum-chemical calculations were performed using GAUSSIAN'98W software.

Iodination of *o*-nitrotoluene (I). *a*. Trifluoromethanesulfonic acid, 7 ml, was cooled to 0–3°C, 0.64 g (1 mmol) of TIG, 0.76 g (2 mmol) of DIH, or 0.91 g (4 mmol) of NIS was dissolved therein, 0.27 g (2 mmol) of *o*-nitrotoluene was added at 0°C, and the mixture was stirred for 15 min at that temperature. The mixture was then poured into 40 ml of an ice–water mixture and extracted with chloroform, and the extract was dried over calcium chloride and analyzed by gas chromatography–mass spectrometry.

b. The procedure was the same as described above in *a*, but sulfuric acid ($d = 1.814$ g/cm^3) was used instead of trifluoromethanesulfonic acid. The reaction time was 30 min with 2 equiv of iodinating agent and 60 min with an equimolar amount of iodinating agent.

Iodination of nitrobenzene (IV). Trifluoromethanesulfonic acid, 7 ml, was cooled to 0–3°C and added under stirring to 0.64 g (1 mmol) of TIG, 0.76 g (2 mmol) of DIH, or 0.91 g (4 mmol) of NIS, and the mixture was stirred until it became homogeneous. The mixture was cooled again to 0°C, 0.25 g (2 mmol) of nitrobenzene was added, and the mixture was shaken for 1 min. When the reaction was complete, the mixture was poured into 40 ml of an ice–water mixture and extracted with methylene chloride, the extract was dried over calcium chloride, the solvent was distilled off, and the residue (3-iodonitrobenzene) was recrystallized from ethanol. Yield 0.99–1.1 g (79–85 %), mp 35–36°C.

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