## Note



# NMR study on the structure and stability of 4-substituted aromatic iodosyl compounds

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Two 4-substituted aromatic iodosyl compounds were investigated with regard to their solubility, stability and chromatographic behaviour. 1-Iodosyl-4-methoxy- and 1-iodosyl-4-nitro-benzene are soluble in methanol and provide acceptable <sup>1</sup>H and <sup>13</sup>C NMR spectra; however, gradual oxidation of the solvent was observed. LC-MS analyses suggest that unlike the parent substance, iodosylbenzene, which has a polymeric structure, both compounds rather exist in the monomeric form. Copyright © 2006 John Wiley & Sons, Ltd.

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#### INTRODUCTION

Hypervalent organic iodine compounds with iodine (III) or (V) as substituent on the phenyl ring has attracted considerable attention in organic chemistry.<sup>1–3</sup> The most important feature of these substances is their electrophilic character, which facilitate many chemical transformations with nucleophilic substrates, in particular, oxidation reactions. For example, the parent substance iodosylbenzene has been proven to be suitable e.g., for, transition-metal-mediated regioselective oxidations of a variety of compounds (summarized in Refs. 1 and 3). The Dess-Martin reagent (1,1,1triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one) has been frequently applied in organic synthesis for the selective oxidation of primary and secondary alcohols to aldehydes or ketones.<sup>4</sup> Diaryliodonium salts also play an important role<sup>1,2</sup> in radiopharmacy particularly in introducing nocarrier-added (n.c.a.) [18F]fluoride into the aromatic ring via nucleophilic <sup>18</sup>F-fluorination, to obtain [<sup>18</sup>F]fluoroarenes.<sup>5</sup>

Iodosylarenes have some special features. EXAFS (extended X-ray absorption fine structure) analysis has revealed that iodosylbenzene consists of a zigzag polymer structure in which monomeric Ph–IO units are linked by intermolecular non-symmetric I–O<sup>TI</sup> bridges.<sup>6</sup> Owing to the polymeric structure, iodosylbenzene is insoluble in all non-reactive solvents. The introduction of electron-withdrawing or donating substituents on the phenyl ring of iodosylbenzene changes the properties of the compound, influencing both the degree of association (R–Ph–IO)<sub>n</sub> and its reactivity as an oxidant. Hence, according to X-ray analysis,

4-chloro- and 4-methyl-iodosylbenzene exist as monomers.<sup>7</sup> Solid-state <sup>13</sup>C NMR spectra<sup>8</sup> indicated sharp signals and some degree of crystallinity for substituted aryliodosyl compounds, such as 1-iodosyl-4-methoxy-benzene, but broadened signals for 1-iodosyl-4-nitro-benzene pointing more likely to an amorphous polymeric structure. Owing to the insolubility in non-reactive NMR solvents and possible oxidation reactions in reactive ones, there are no solution NMR data available for substituted aromatic iodosyl compounds.

In connection with radio-high performance liquid chromatography (radio-HPLC) investigations on astatine-211 labelled 4-substituted aromatic compounds and assumed astatosyl species Ph–AtO (unpublished data), we were interested in the solubility and chromatographic behaviour of selected aromatic iodosyl compounds for comparison.

Hence, 1-iodosyl-4-methoxy-benzene (1) and 1-iodosyl-4nitro-benzene (2) as two simple model substances containing *para*-substituents, with electron-donating and withdrawing substituents, respectively, were investigated. In this study, we present the <sup>1</sup>H and <sup>13</sup>C NMR spectra of these two iodosylarenes and data concerning their stability in CD<sub>3</sub>OD solutions (Scheme 1).

#### **RESULTS AND DISCUSSION**

1-Iodosyl-4-methoxy-benzene and 1-iodosyl-4-nitro-benzene were prepared according to the literature by oxidation of the corresponding iodo aromatics with sodium periodate NaIO<sub>4</sub> and sodium perborate NaBO<sub>3</sub> in glacial acetic acid, respectively, followed by an alkaline treatment of the isolated (diacetoxyiodo)benzene derivatives<sup>9–11</sup> (Scheme 2).

Substituted iodyl aromatics (R–Ph–IO<sub>2</sub>) can also be obtained from iodo compounds and sodium periodate but require more drastic reaction conditions.<sup>10</sup> Compounds **1** 



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Scheme 1. lodosyl compounds studied with numbering of C/H atoms (see Table 1).

and **2** are white and yellow-orange solids, respectively. The analytical data available for the two substances are limited, and mainly consist of infrared spectroscopy.<sup>12</sup> The infrared spectra are characterized by I=O vibrations in the range from 720 to 790 cm<sup>-1</sup>; and all other vibrations are very similar to those of the substituted iodo aromatics.<sup>13</sup>

Iodosylbenzene is insoluble in weakly polar solvents. Its solubility in anhydrous methanol is the result of the reaction producing (dimethoxy)iodobenzene  $PhI(OCH_3)_2$ .<sup>14</sup> The solubility of iodosylbenzene in acetic acid is based on its conversion to iodosylbenzene diacetate  $PhI(OAc)_2$ .<sup>15</sup>

Therefore, we tested the solubility of freshly prepared 1 and 2 in more polar solvents such as deuterated dimethylsulfoxide (DMSO), acetonitrile and methanol, monitoring the solutions by <sup>1</sup>H NMR. DMSO proved to be inapplicable; since it reacted with 2 causing a complete reduction of the iodosyl group. Only the <sup>1</sup>H NMR signal characteristics of 1-iodo-4-nitro-benzene were detected. The solubility of 1 in acetonitrile was too low, whereas 2 could be largely dissolved only by heating (5 min at 70  $^{\circ}$ C), thereby changing the orange red suspension to a pale yellow solution. According to the <sup>1</sup>H NMR spectrum, only the signals of 1-iodo-4-nitro-benzene were observed suggesting that acetonitrile was also oxidized. To our knowledge, the direct oxidation of nitriles by polyvalent iodine compounds has not been reported except for the reaction of aldoximes with (dichloroiodo)benzene (PhICl<sub>2</sub>), which afforded reactive, mostly unstable, nitrile oxides and corresponding dimerization products via 1,3 cycloaddition.<sup>16</sup>

The two substances are moderately soluble in methanol and provided reasonable <sup>1</sup>H NMR spectra (Table 1) with a significant downfield shift of aromatic proton signals *versus* the iodo compounds. This is consistent with the distinct electron-withdrawing effect of the iodosyl group as expected from calculated group electronegativities.<sup>17</sup> Methanolic solution of 1-iodosyl-4-nitro-benzene has no long-term stability. After it was allowed to stand for several hours at room temperature, the <sup>1</sup>H NMR signals of 1-iodo-4-nitro-benzene appeared and increased steadily (Figs 1, 2). This can be explained by the fact that **2** gradually MRC

oxidizes the solvent to form formaldehyde and/or formic acid, following approximately a pseudo first-order kinetics (Fig. 2). It is somewhat surprising that the relative oxidation-resistant nitrile group of acetonitrile was more easily oxidized by **2** than methanol. As expected, warming of the mixture accelerated the reaction. According to the literature the oxidation of primary alcohols to aldehydes or carboxylic acids is typical for iodosylbenzene derivatives.<sup>1,18</sup> The oxidation of primary alcohols, for example, in the presence of a ruthenium catalyst has been reported.<sup>19</sup> The disproportionation of **2** into 4-nitro-iodylbenzene and 1-iodo-4-nitro-benzene<sup>15</sup> could not be observed; the corresponding aromatic proton signals in the <sup>1</sup>H NMR were absent.

1-Iodosyl-4-methoxy-benzene was less reactive towards methanol; after 24 h at r.t., the <sup>1</sup>H NMR spectrum remained unchanged and only 18% of **1** was converted to 1-iodo-4-methoxy-benzene after warming for 1.5 h at 60 °C. The stability of the neat solid compounds is similar; while **1** can be stored under nitrogen atmosphere at approx. 0 °C over months, compound **2** was largely converted to the iodo compound within several weeks (under loss of oxygen?). Unlike iodosylbenzene, the two compounds did not react with methanol to give the iodosyl-dimethoxide derivative (see above). Attempts with stirring in methanol at r.t. or at elevated temperature for 1 h under nitrogen afforded always mixtures of iodosyl and iodo compounds in highly varying compositions.

The <sup>13</sup>C NMR spectra (Table 1) confirm the substantial decrease of the strong shielding of the *ipso*-carbon atom by iodine, typical for aryl iodides and described as a general feature for a wide range of substituted polyvalent iodine compounds.<sup>7</sup>

 Table 1. <sup>1</sup>H and <sup>13</sup>C NMR data of iodosyl derivatives 1 and 2;

 the assignment of the latter is based on APT experiment

H/C CD <sub>3</sub> OD 1-Iodosyl-4-methoxy-benzene (1) 1 2 3 5 1-Iodosyl-4-nitro-benzene (2) 1 2 8.33 3 8 2		
CD <sub>3</sub> OD         1-Iodosyl-4-methoxy-benzene (1)         1         2       7.92         3       7.02         4         5         1-Iodosyl-4-nitro-benzene (2)         1         2       8.32         3       8.22	$^{1}\mathrm{H}$	<sup>13</sup> C
1-Iodosyl-4-methoxy-benzene (1) 1 2 3 3 4 5 1-Iodosyl-4-nitro-benzene (2) 1 2 8.37 3 8 2		
1 2 7.92 3 7.02 4 5 1-Iodosyl-4-nitro-benzene (2) 1 2 8.33 3 8 2		
2 7.92 3 7.02 4 5 1-Iodosyl-4-nitro-benzene (2) 1 2 8.33 3 8.22	_	113.2
3 7.0 4 5 1-Iodosyl-4-nitro-benzene (2) 1 2 8.3 3 8.2	3–7.97, AA'XX'	135.6
4 5 1-Iodosyl-4-nitro-benzene (2) 1 2 8.3 3 8.2	7–7.11, AA'XX′	117.4
5 1-Iodosyl-4-nitro-benzene (2) 1 2 8.3 3 8.2	-	163.3
1-Iodosyl-4-nitro-benzene (2) 1 2 8.3 3 8.2	3.88	56.2
1 2 8.3 3 8.2		
2 8.3 3 8.2	-	127.6
3 8.2	7–8.41, AA'XX'	133.9
0.1	5–8.29, AA'XX'	126.5
4	_	150.8



Scheme 2. Preparation of 1-iodosyl-4-methoxy-benzene (1) and 1-iodosyl-4-nitro-benzene (2).





Figure 1. <sup>1</sup>H NMR spectrum of freshly dissolved 1-iodosyl-4-nitro-benzene in CD<sub>3</sub>OD. Inset A: after 3 h, inset B: after 96 h.



Figure 2. Temporal decrease of the concentration of 2 in CD<sub>3</sub>OD at ambient and elevated temperature.

Thin layer chromatography (TLC) of 1 and 2 points to a much higher polarity of these substances in comparison to the iodo compounds. To confirm this and to identify the degree of aggregation for compounds 1 and 2, we performed HPLC-MS analyses. Both compounds demonstrated very different retention times from the iodo- and all other halogen reference substances. In the ESI-MS spectra we found molecular peaks of medium intensity, strong peaks for the  $[R - Ph - I]^+$ fragment, and weak signals probably consistent with dimeric molecules but no evidence for higher units. Interestingly, distinct fragment peaks were observed for compound 1 that match with corresponding iodoniumions  $[(R-Ph)_2 - I]^+$ . These results are less compatible with a polymeric structure, confirming that the structure of iodosylbenzene is different from these substituted derivatives. This suggests that 1 and 2 exist rather as monomeric units or are depolymerized

by methanol without further reaction. Regarding the two resonating structures I=O  $\leftrightarrow$  I<sup>+</sup>-O<sup>-</sup>, the iodine-oxygen bond has probably at least a semipolar character.<sup>20</sup>

The  $\delta$  values of the aromatic protons for **2** are clearly shifted downfield compared to **1**, i.e. the electron density at the C–H bonds is reduced because of the –I, –M effect of the nitro group. The electron density at the iodine–oxygen bond in 1-iodosyl-4-nitro-benzene should also be decreased, thus leading to a facilitated release of oxygen and to an increased oxidizing effect. Conversely, electron-donating substituents are expected to enhance the nucleophilicity of R–Ph–IO and possibly promote the association tendency of monomeric units.<sup>21</sup> However, both electron-donating (–OCH<sub>3</sub>) and electron-withdrawing (–NO<sub>2</sub>) substituents seem to affect similarly the iodosyl group. Gao *et al.*<sup>21</sup> observed such an effect of enhanced reactivity towards metal carbonyls.

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On the other hand, the function of iodosylbenzene as an oxygen donor for the epoxydation of stilbene was completely stopped by insertion of a *para*-nitro group.<sup>11</sup>

## EXPERIMENTAL

Chemical reagents were purchased from standard commercial suppliers and were used without further purification. NMR spectra were recorded with a Varian Mercury-VX 400 spectrometer operating at 400 MHz for <sup>1</sup>H and 100 MHz for <sup>13</sup>C and with a Varian Gemini spectrometer at 300 MHz (<sup>1</sup>H) at 26 °C. Five millimetre sample tubes were used with sample concentrations of 5-6 mg/0.7 ml (<sup>1</sup>H) and ca 12–15 mg/0.7 ml (<sup>13</sup>C), respectively. Chemical shifts are reported as  $\delta$  values (ppm) with reference to the solvent signals of CD<sub>3</sub>OD ( $\delta$  3.31 ppm for <sup>1</sup>H and 49.0 ppm for <sup>13</sup>C). Melting points were determined with a Büchi B-545 apparatus. IR spectra were measured on KBr using a Perkin Elmer FT-IR spectralphotometer system 2000. LC-MS chromatograms were obtained with a Mariner Biospectrometry Workstation (Applied Biosystems) using a Zorbax C8 column (4.6 mm  $\times$  15 cm) and a mixture of MeOH/H<sub>2</sub>O 30:70 as eluent with 5 mmol ammonium acetate. Additional ESI mass spectra were obtained using a Triple-Quadro LC-MS device (Micromass).

### 1-Iodosyl-4-methoxy-benzene (1)

Yield: 88%; white to pale yellow solid; mp: *ca.* 190–200 °C (gradual melting, decomp.); IR (KBr)  $\nu$ : 715, 768 cm<sup>-1</sup> (only absorption bands in the characteristic range for hypervalent iodine compounds are given, see above); HPLC-MS:  $R_t$  7.2 min;  $R_t$  15.5 min (iodonium compound); ESI-MS m/z: 251 [M]<sup>+</sup>, 234 [CH<sub>3</sub>O–Ph–I]<sup>+</sup>, 341 [(CH<sub>3</sub>O–Ph–)<sub>2</sub>I]<sup>+</sup>.

### 1-Iodosyl-4-nitro-benzene (2)

Yield: 90%; yellowish orange solid; mp: 80–81 °C (decomp.); IR (KBr) v: 780 cm<sup>-1</sup> (only absorption bands in the characteristic range for hypervalent iodine compounds are given (see above); HPLC-MS:  $R_t$  6.6 min.; ESI-MS m/z: 266[M]<sup>+</sup>, 249 [O<sub>2</sub>N–Ph–I]<sup>+</sup>.

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