Halogen Bonds of 4-Iodosydnones in Solution Deduced from ^{13}C-NMR Spectra

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The ability of 4-iodosydnones to form halogen bonds with Lewis bases in solution was deduced from significant changes in the ^{13}C-NMR chemical shift of the carbon atom of the sydnone ring which is bonded to iodine.

Keywords: halogen bonding, 4-iodosydnone, ^{13}C-NMR spectroscopy

In 2013 Desiraju et al. [1] presented a definition of the halogen bond (XB) as follows *A halogen bond occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity.* As in the case of the hydrogen bond, the halogen bond, which is a non-covalent interaction, is represented by three dots in the formalism R–X⋯Y, where X is a halogen atom (X=F, Cl, Br, I) from an organic halide but may also be from a halogen (I_2, Br_2) or interhalogen molecules (ICl, IBr). The Lewis base Y (the XB acceptor) can be atoms with a lone pair (nitrogen, oxygen and halogen), anions (X^-, RO^-) or a π-system. Halogen bonding has received significant interest in the last decade and its importance in the fields of supramolecular chemistry, crystal engineering, liquid crystals and biochemistry is well recognized and as a consequence a large number of reviews and articles on this topic have been reported [2-7].

The existence of halogen bonding in the solid state was evidenced by X-ray crystallography, the main criterion being that the distance between the atoms X⋯Y should be shorter than the sum of the van der Waals radii of atoms X and Y. Establishment of the presence of halogen bonding in solution is rather scarce and the methods which have been applied are limited by poor sensitivity. Recently, Erdely [8,9] summarized in two recent reviews a critical evaluation of physicochemical methods used for detecting halogen bonds in solution and determining their nature. The applications of halogen bonds in solution were discussed by Jentzsch in 2015 [10].

Sydnones (fig. 1) are a class of stable mesoionic compounds with the 1,2,3-oxadiazole framework that are prepared by nitrosation and cyclisation of the corresponding N-substituted α-amino acids [11-20] Sydnones present interesting biological and chemical properties and they are starting materials for the preparation of other heterocyclic compounds such as pyrazoles, indazoles and carbazoles. The transformation of sydnones into the corresponding 4-halogenosydnones (R^2= Cl, Br, I) was realized by using a variety of halogenating reagents [11, 14-20] and this motivated us to investigate the capacity of 4-iodosydnones to form halogen bonding interactions in solution.

Herein is reported a qualitative study based on ^{13}C-NMR spectroscopy regarding the capacity of 4-iodosydnones (Lewis acids) to establish halogen bonding with Lewis bases in solution.
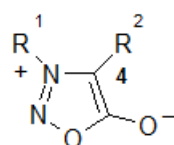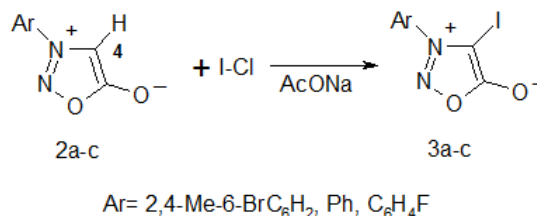

Fig. 1. The structure of sydnones

Sydnones: $R^1 \neq H$

Experimental part

The NMR spectra were recorded on a Varian Gemini 300 BB instrument, operating at 300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR.

The 4-iodosydnones **3a-c** used in this study were obtained by iodination of 3-arylsydnones **2** at the C-4 position. The iodination was performed according to the literature or *via* our procedures by using iodine monochloride or N-iodosuccinimide in acetic acid medium (scheme 1) [14-20].The characterization of 4-iodosydnones **3a,b** was reported in the literature [14,15] and data for **3c** will be published elsewhere.

Ar= 2,4-Me-6-BrC$_6$H$_2$, Ph, C$_6$H$_4$F

Scheme 1. Iodination of sydnones with ICl

Results and discussions

It is well established that the strength of halogen bonds decreases in the order I >Br>Cl>F which represents the capacity of halogens to form non-covalent interactions. Based on this rule we envisaged that in the series of 4-halogenosydnones, 4-iodosydnones provided the best chance of detecting halogen boding in solution by C-NMR spectra. An additional reason for this choice was the significant modification of the chemical shifts in the case of C-NMR spectra of iodoacetylenes recorded in deuterated dimethylsulfoxide or pyridine [21-27].

The NMR study for the detection of halogen bonding in solution was carried out in neat solvents of varying polarity and basicity such as pyridine-d5, dimethylsulfoxide-d6, $CDCl_3$ and C_6D_6. Based on the high solubility of 4-iodosydnones in $CDCl_3$ the majority of the experiments were conducted at room temperature in this solvent. Another advantage of using $CDCl_3$ is that its action as a

halogen bond donor in the presence of Lewis bases is weak [7].

Initially, the proton and carbon NMR spectra of 4-iodosydnones were recorded in CDCl$_3$ at room temperature. After the NMR spectra were recorded, the Lewis base was added to the solution of the 4-iodosydnone in CDCl$_3$ and the NMR spectra of the resultant solutions were recorded under similar conditions. As nitrogen Lewis bases, triethylamine, deuterated pyridine (Py-d5) and 4-diazabicyclo[2.2.2]octane (DABCO) were used. Dimethyl-sulfoxide-d6 was selected as a Lewis base having an oxygen donor atom. Firstly, spectra were recorded at 2:1 molar ratio between Lewis base and iodosydnone. The inspection of ^{1}H-NMR spectra of 4-iodosydnones in CDCl$_3$ and CDCl$_3$+Lewis base showed no evidence for the presence of halogen bonds in solution. However, examination of the ^{13}C-NMR data (table 1) clearly indicated a significant change to higher frequency for chemical shifts of the carbon atom at sydnone-ring position 4, which is bonded to the iodine atom. The difference (Δ) between chemical shifts of C-I measured in CDCl$_3$+Lewis base and CDCl$_3$ is in all cases more than 1.4 ppm. For the other carbon atoms of the iodosydnone molecule the differences in the values of the chemical shifts are usually under 0.5 ppm.

Table 1 presents the change in the chemical shift of the carbon atom bonded to the iodine atom of the 4-iodosydnone **3a** and it is evident that this parameter measured in CDCl$_3$+Lewis base increases with the increase in the concentration of the Lewis base, attaining a maximum value in the neat Lewis base.

The ^{13}C-NMR experiments performed with 4-iodo-3-phenylsydnone **3b** and various Lewis bases (table 2) indicated a similar behavior as in the case of 4-iodo-3-(2,4-dimethyl-4-bromophenyl)sydnone.

As mentioned above, 4-iodosydnones exhibited low solubility in non-polar NMR deuterated solvents. However, we found in our sydnone library that 4-iodo-3-(fluorophenyl)sydnone **3c** is soluble in deuterated benzene. The ^{13}C-NMR spectra recorded in C$_6$D$_6$ at room temperature and at two concentrations of triethylamine showed a similar behaviour as in case of CDCl$_3$. In comparison with deuterated benzene (δ_{C-I}=52.3 ppm) the chemical shift of atom C4 of the sydnone ring at two ratios of triethylamine vs. sydnone ($c_2 > c_1$) indicated the change of chemical shift to δ_{C-I}=55.2 ppm and δ_{C-I}=58.0 ppm, respectively.
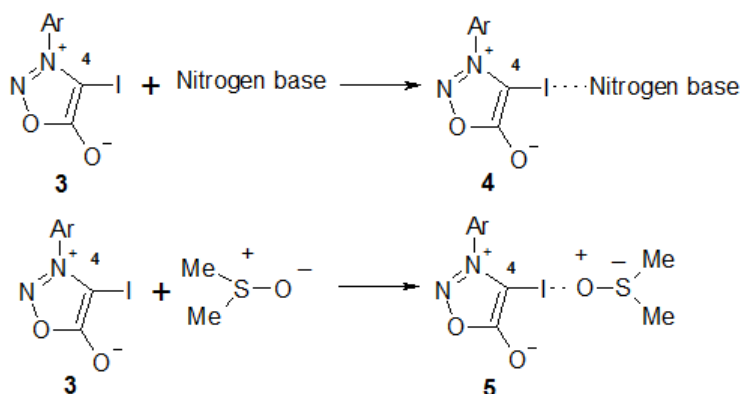
The ^{13}C-NMR experiments indicated a strong change in chemical shifts of the carbon bonded to the iodine atom in the presence of Lewis base (tables 1 and 2). The significant

Table 1

CHANGE OF THE CHEMICAL SHIFT OF THE CARBON ATOM BONDED TO IODINE IN THE PRESENCE OF LEWIS BASES.

Entry	Solvent; Molar Ratio: base/sydnone	δ_{C-I} ppm	Chemical shifts for aromatic carbon atoms (phenyl) δ_{ppm}					
1	CDCl$_3$ neat	52.8 Δ=0	169.0	119.8	131.3	132.1	136.6	144.6
2	CDCl$_3$+Py-d$_5$; 2/1	54.4 (Δ=1.6)	169.2;	119.7;	131.2;	131.9;	136. 5;	144.3
3	CDCl$_3$+Py-d$_5$; 10/1	56.8 Δ=4.0	169.4	119.4	130.9	131.6	136. 3	144.1
4	Py-d$_5$ neat	60.9 Δ=8.1	170.3	120.0	131.6	131.6	136.9	144.8
5	CDCl$_3$ + Et$_3$N; 2/1	54.2 Δ=1.4	168.9	119.8	131.2	132.0	136. 6	144.4
6	CDCl$_3$ + Et$_3$N; 10/1	56.2 Δ=3.4	169.4	119.8	131.1	131.8	136. 5	144.2
7	CDCl$_3$ + Et$_3$N; 30/1	58.3 Δ=5.5	169.6	119.7	130.8	131.6	136.4	143.8
8	CDCl$_3$ + DABCO; 2/1	58.5 Δ=4.4	170.0	119.8	131.1	131.4 131.6	136.5	144.0
9	CDCl$_3$ + DMSO-d6; 2/1	52.4 Δ=1.9	168.9	119.2	130.5	131.4 131.7	136.5	144.8
10	DMSO-d6 neat	59.4 Δ=6.6	168.9	119.2	130.5	131.4 131.7	136.5	144.8

Table 2

THE CHEMICAL SHIFT OF THE CARBON ATOM BONDED TO IODINE FOR 4-IODO-3-PHENYLSYDNONE **3b**

Solvent	CDCl$_3$	CDCl$_3$ +Et$_3$N	CDCl$_3$ +Pyd-5	CDCl$_3$ +Pyd-5	Py-d5	CDCl$_3$+ DMSO-d6	DMSO-d6
Ratio base/3b	neat	2/1	2/1	10/1	neat	2/1	neat
δ_{C-I} ppm (Δ)	50.5 Δ=0	54.0 Δ=3.5	53.1 Δ=2.6	54.0 Δ=3.5	59.0 Δ=8.5	52.4 Δ=1.9	58.0 Δ=7.5

Scheme 2. Complexation of 4 iodosydnones with Lewis bases

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variation of the chemical shift for C-I can be explained by non-covalent interaction established between the iodine atom as Lewis acid and Lewis bases represented by dimethylsulfoxide, aliphatic amines and a heteroaromatic amine (scheme 2). A similar strong effect in the presence of Lewis bases was reported for α-carbon chemical shifts of iodoalkynes [21-27].

As in the case of iodoacetylenes [21-27] the phenomenon is explained by complexation of iodine with deuterated basic solvents (pyridine-d5, dimethysulfoxide-d6) or with the Lewis bases added to the deuterated solvents. In more basic solvents the chemical shifts for C-I appear at higher frequency. Based on the literature and our ^{13}C-NMR experiments, formation of the complexes **4** and **5** in solution indicated that 4-iodosydnones are sufficiently Lewis acidic to act as donors in halogen bonding.

Conclusions

The strong influence of Lewis bases on chemical shifts in ^{13}C-NMR spectra for the carbon atom bonded to iodine of the 4-iodosydnones reported in this study is good evidence for complexation reaction between the iodine atom and Lewis bases. The significant change of ca. 6.6-8.5 ppm for the C-I shift in the neat Lewis bases indicated that the 4-iodosydnones are halogen bond donors and strong Lewis acids.

The qualitative ^{13}C-NMR study reported led us to conclude that 4-iodosydnones form halogen bonds with Lewis bases in solution. Our investigation by X-ray diffraction regarding the presence of halogen bonds in the solid state of 4-halogenosydnones is underway.

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