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NMR spectroscopy study of 2-methylbenzoxazolium salts hydroxylation in DMSO-d_6 solution

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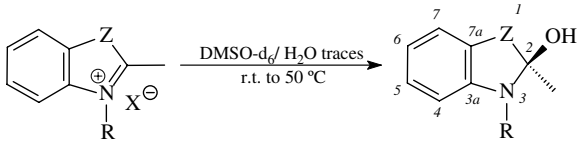
Abstract—2-Methylbenzoxazolium salts showed an unexpected transformation at room temperature, promoted by residual water present in dimethyl sulfoxide. This transformation was followed up inside of an NMR sample tube using DMSO-d_6 as solvent, in a series of representative quaternary ammonium salts with carboxymethyl, ethyl, pentyl and decyl *N*-alkyl chains, resulting in an exclusive product. The corresponding benzothiazolium and benzoselenazolium salts presented a similar behavior after heating at a temperature of 50 °C with the addition of one drop of D_2O for the first of these two salts. This reaction could play a very important role in explaining certain secondary reactions occurring in the preparation of compounds where these salts are precursors, classically in cyanine dye synthesis. Four new benzoxazolols were characterized by NMR spectroscopy and HR FAB-MS.

In our previous work, some *N*-alkylquaternarium ammonium salts bearing benzoxazole **1**, benzothiazole **2** and benzoselenazole **3**, and containing a methyl group in position 2 with respect to the ammonium atom and to the ethyl, pentyl, hexyl, and decyl *N*-alkyl chains, were fully characterized physically and spectroscopically.[1] These heterocyclic salts are typical precursors of cyanine dye,[2] which makes any reaction related to the dye's preparation or transformation into side products very important. Nevertheless, although these typical cyanine precursors are quite stable whether in crystalline form or in solution, attempts to perform the ^1H and ^{13}C NMR characterization of benzoxazolium salts **1** in DMSO-d_6 always yield unexpected results. In different experiments carried out from the same sample, the ^1H and ^{13}C NMR spectra revealed either a mixture of two products in varying relative amounts or just one of them exclusively, depending on the time between preparation of the sample and acquisition of the NMR spectrum.

On the other hand, the ^1H and ^{13}C NMR characterization of the same salts performed in $CDCl_3$ revealed that they are constituted by just one of the compounds present in the DMSO-d_6 solution mixture. Also unexpected were the ^1H NMR data for several benzoxazolium salts in DMSO-d_6 reported in the literature,[3] identical to the data we obtained in $CDCl_3$, which did not mention the appearance of a mixture of two products during the NMR acquisition.

The observation of an 18-*m*/*z* increment on the HR FAB-MS of the new compounds **4** in relation to the ammonium salts **1**, clearly indicated a complete transformation in situ into its hydroxylated form (Scheme 1).

The unexpected product also presented two geminal *N*-methylenic non-equivalent protons between 3–5 ppm, which proved to be characteristic of these hydroxylated benzoxazoles.



1(Z=O), **2**(Z=S), **3**(Z=Se)

4(Z=O), **5**(Z=S), **6**(Z=Se)

a (R=CH_2CO_2H, X=Br); **b** (R=CH_2CH_3, Z=I); **c** [R=$(CH_2)_4CH_3$, Z=I]; **d** [R=$(CH_2)_9CH_3$; Z=I)

Scheme 1. Hydroxylation of 2-methybenzoxazolium salts **1**–**3**.

Keywords: Hydrolysis; Benzoxazolium; Benzoxazolol; Ammonium quaternary salts; Spectroscopic characterization; NMR.
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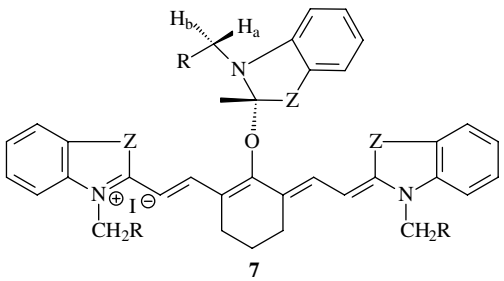
To the best of our knowledge, there are just a few examples in the literature describing 2-hydroxy and 2-alcoxy 2-methylbenzoxazoles. Metzger and coworkers[4] observed the formation of 2-alcoxybenzothiazolines in solution, which were not isolable due to their instability. However, Oliveros and Wahl[5] were able to isolate and ^{1}H NMR characterize a series of four 1-alkyl-2-alcoxy-2-methylbenzoxazolines. Both authors used sodium or potassium hydroxide to catalyze this reaction. Two additional example include the substituted heptamethinecyanine dyes **7** (Fig. 1) and the intermediate 2-methylbenzoxazolol, postulated as possibly involved in the formation of the first.[6] Another, related example is the addition reaction of hydroxide or ethoxide ion into the C-2 of the polymethine chain benzoindolium heptamethinecyanine dyes, once again by the use of potassium hydroxide in an aqueous alcohol solution.[7]

The benzoxazolium salts **1** were readily and completely converted at room temperature in 4–24 h, to exclusively yield the hydroxylated derivatives **4**. The reaction course was easily and unambiguously followed up by the transformation of both aliphatic and aromatic ^{1}H and ^{13}C signals of the benzoxazolium salts **1** into the corresponding hydroxylated derivative **4** signals, in distinct and separated regions. Another characteristic feature of this reaction was the decreasing intensity of the residual signal of the water, due to its consumption during the reaction (at $\delta = 5.67$ ppm, Fig. 2a–c). In some cases, we observed a simultaneous shift to higher fields, implying an interaction between the water and the salt along with the consumption of the water.

On the other hand, benzothiazolium **2** and benzoselenazolium **3** salts did not show any conversion at room temperature. Nevertheless, when heated to 50 °C, the benzoselenazolium salts **3** were converted in 12–26 h. The benzothiazolium salts **2** did not show any transformation, unless one drop of D_2O was added at 50 °C; at this point, it was totally transformed after only 3–25 days. Both salts **2** and **3** yielded the hydroxylated form in a more complex mixture. In these cases, the presence of the benzoxazolol derivative was revealed by the presence of the two typical geminal non-equivalent protons. Since the NMR analysis showed a reaction mixture constituted by more than one product, the hydroxylated products **5** and **6** were not spectroscopically characterized.



7

Z = CH=CH, O, S, Se; R=$CH_2)_nCH_3$ (n=0, 3, 8)

Figure 1. Substituted heptamethinecyanine dyes.[6]

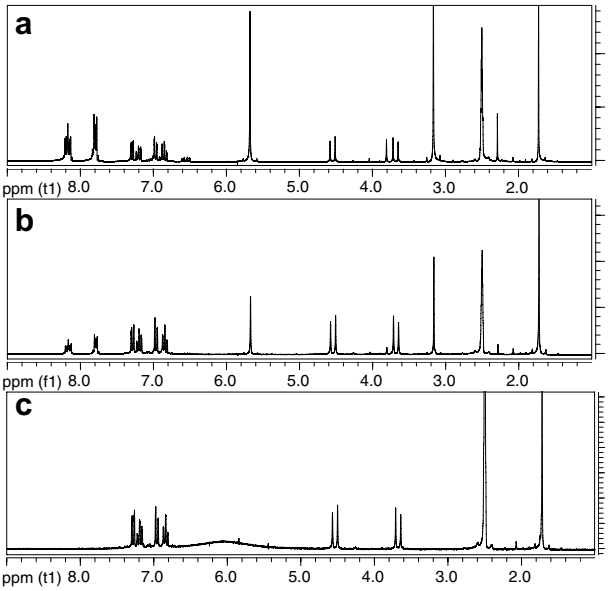


Figure 2. NMR spectra of benzoxazolium salt **1a** in DMSO-d_6 solution: 4 min (a), 2 h (b) and 4 h (c) after the sample tube preparation.

Generally speaking, the following order can be established for the reaction rates regarding the aromatic moiety: **1** (X = O) >>> **3** (X = Se) > **2** (X = S). The analysis of the influence of the aromatic nature shows that the presence of oxygen in the heterocyclic moiety is decisive for the reaction rate and reaction effectiveness, especially at room temperature and in the absence of added water. The presence of the selenazole or sulfur atom is only important at higher temperatures and, for the last salt case, in the presence of higher water concentrations. Regarding the aliphatic nature of the *N*-alkyl chain, **a** ($R = CH_2CO_2H$) ≫ **b**–**d** (R = alkyl), reflecting the electronic effect of the electron-withdrawing carboxyalkyl group.

The *N*-alkyl and *N*-carboxyalkylbenzoazolium salts **1**–**3** were prepared as already described.[1,8]

Benzoxazolols **4** were characterized by ^{1}H and ^{13}C NMR in DMSO-d_6 solution after the complete conversion in situ inside of the NMR sample tube.[9] All the new compounds characterized presented a purity >95% pure, in solution, by ^{1}H NMR.

The time registered for the complete conversion reflected the point when a negligible signal of the starting salt was observed in the spectra, which was generally much less than 5%. The aliphatic and aromatic proton and carbon shifts were assigned by analysis of the multiplicity and relative integration of the signals. These attributions were also confirmed or unequivocally achieved through some heteronuclear one- and multiple-bond correlation experiments. The unambiguous identities of these derivatives were established by the High Resolution Mass Spectra (HR FAB-MS) for all benzoxazolols dissolved in DMSO-d_6 that are described here.[9]

Typically, benzoxazolols **4** present two geminal *N*-methylenic non-equivalent protons between 3 and 5 ppm with a geminal coupling constant of 13.3–13.8 Hz and 17.3–17.5 Hz for the *N*-alkyl derivatives **4b–d** and for the carboxymethyl derivative **4a**, respectively. This pattern proves to be characteristic for these benzoxazolols and resembles the pattern found in the *N*-ethyl group (protons H_a and H_b) present in the third oxygenated heterocyclic moiety of the rigidified heptamethinecyanine **7** (Fig. 1).[6]

In conclusion, the transformation of benzoxazolium, benzothiazolium and benzoselenazolium salt series, which is promoted by residual water present in dimethyl sulfoxide, proves to depend on the nature of the aromatic moiety and, to a lesser extent, on the aliphatic nature of the *N*-alkyl chain. This observation could play a very important role in reactions where these salts are precursors, classically in cyanine dye synthesis.[2] The occurrence of this hydroxylation reaction could reasonably explain the formation of secondary products in reactions where these salts are present with concomitant yield reduction of the desirable and expected products. This side reaction could be especially important in reactions where polar solvents are used without the precaution of removing residual water traces.

Acknowledgements

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9. DMSO-d_6 was purchased from Sigma–Aldrich and was used without further purification. High Resolution Fast Atom Bombardment Mass Spectra (HR FAB-MS) of benzoazoles DMSO-d_6 solutions were recorded in a Micromass AutoSpec M, operating at 70 eV, using a matrix of 3-nitrobenzyl alcohol (3-NBA). ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 solutions on a Brüker ACP 250 (250.13 and 62.90 MHz) spectrometer. Chemical shifts are reported in ppm and coupling constants (*J*) are given in Hz. HMQC, HMBC, and COSY spectra were acquired on a Brüker ARX 400 (400.13 and 100.62 MHz). Generally, 10 mg of salts **1–3** was dissolved in 0.5 ml of DMSO-d_6 in a sample tube and the ^{1}H NMR spectra were acquired at regular intervals depending on the time of transformation. When a temperature of 50 °C was used, the sample tubes were kept in a temperature-controlled bath during the time of experimentation. For salts **2**, a drop of D_2O was added to the specimen tube. *(2-Hydroxy-2-methylbenzoxazol-3-yl)acetic acid* (**4a**): 4 h at room temperature. ^{1}H NMR (250.13 MHz, DMSO-d_6) δ (ppm): 1.72 (3H, s, 2-CC*H*$_3$), 3.68 (1H, d, $J = 17.3$, 3-NC*H*H), 4.54 (1H, d, $J = 17.5$, 3-NCH*H*), 6.84 (1H, dt, $J = 7.6$, 1.3 Hz, 5-C*H*), 6.96 (1H, dd, $J = 8.0$, 1.3 Hz, 7-C*H*), 7.20 (1H, dt, $J = 8.0$, 1.8 Hz, 6-C*H*), 7.29 (1H, dd, $J = 7.8$, 1.8 Hz, 4-C*H*), 10.09 (1H, br s, OH, change with D_2O), 12.81 (1H, br s, CO_2H, change with D_2O). ^{13}C NMR (62.90 MHz, DMSO-d_6) δ (ppm): 21.3 (2-C*C*H$_3$), 49.7 (3-N*C*H$_2$CO$_2$H), 116.8 (7-*C*H), 119.6 (5-*C*H), 131.5 (6-*C*H), 132.0 (3a-*C*), 132.1 (4-*C*H), 152.8 (7a-*C*), 170.1 (2-*C* or *C*O), 171.4 (2-*C* or *C*O). HR FAB-MS: 210.0765 (M^+, $C_{10}H_{12}NO_4$); calcd 210.0766; 3-ethyl-2-methyl-2,3-dihydrobenzoxazol-2-ol (**4b**): 24 h at room temperature. ^{1}H NMR (250.13 MHz, DMSO-d_6) δ (ppm): 0.95 (3H, t, $J = 7.3$ Hz, CH$_2$C*H*$_3$), 1.65 (3H, s, 2-CC*H*$_3$), 3.34 (1H, dq, $J = 13.8$, 7.2 Hz, 3-NC*H*H), 3.70 (1H, dq, $J = 13.3$, 7.3 Hz, 3-NCH*H*), 6.84 (1H, dt, $J = 7.6$, 1.4 Hz, 5-C*H*), 6.95 (1H, dd, $J = 8.0$, 1.3 Hz, 7-C*H*), 7.12 (1H, dd, $J = 8.0$, 1.8 Hz, 4-C*H*), 7.18 (1H, dt, $J = 7.6$, 1.8 Hz, 6-C*H*), 8.15 (1H, br s, OH, change with D_2O). ^{13}C NMR (62.90 MHz, DMSO-d_6) δ (ppm): 12.8 (CH$_2$*C*H$_3$), 21.9 (2-C*C*H$_3$), 41.8 (3-N*C*H$_2$), 116.6 (7-*C*H), 119.5 (5-*C*H), 129.0 (6-*C*H), 129.3 (3a-*C*), 129.8 (4-*C*H), 153.3(7a-*C*), 169.1 (2-*C*). HR FAB-MS: 180.1028 (M^+, $C_{10}H_{14}NO_2$); calcd 180.1025. *2-Methyl-3-pentyl-2,3-dihydrobenzoxazol-2-ol* (**4c**): 12 h at room temperature. ^{1}H NMR (250.13 MHz, DMSO-d_6) δ (ppm): 0.80 (3H, t, $J = 6.6$ Hz, CH$_2$C*H*$_3$), 1.18–1.26 (4H, m, (C*H*$_2$)$_2$CH$_3$), 1.35 (2H, qt, $J = 7.0$, C*H*$_2$(CH$_2$)$_2$CH$_3$), 1.65 (3H, s, 2-CC*H*$_3$), 3.26 (1H, dt, $J = 13.5$, 7.2 Hz, 3-NC*H*H), 3.67 (1H, dt, $J = 13.5$, 7.5 Hz, 3-NCH*H*), 6.51 (1H, br s, OH, change with D_2O), 6.83 (1H, dt, $J = 7.5$, 1.3 Hz, 5-C*H*), 6.95 (1H, dd, $J = 8.0$, 1.0 Hz, 7-C*H*), 7.10 (1H, dd, $J = 7.8$, 1.3 Hz, 4-C*H*), 7.17 (1H, dt, $J = 7.6$, 1.6 Hz, 6-C*H*). ^{13}C NMR (62.90 MHz, DMSO-d_6) δ (ppm): 13.8 (CH$_2$*C*H$_3$), 21.9 (2-C*C*H$_3$), 21.9 (*C*H$_2$CH$_3$), 26.9 (*C*H$_2$CH$_2$CH$_3$), 28.5 (*C*H$_2$(CH$_2$)$_2$CH$_3$), 46.8 (3-N*C*H$_2$), 116.6 (7-*C*H), 119.5 (5-*C*H), 128.9 (6-*C*H), 129.6 (3a-*C*), 129.7 (4-*C*H), 153.2 (7a-*C*), 169.3 (2-*C*). HR FAB-MS: 222.1494 (M^+, $C_{13}H_{20}NO_2$); calcd 222.1494. 3-Decyl-2-methyl-2,3-dihydrobenzoxazol-2-ol (**4d**): 8 h at room temperature. ^{1}H NMR (250.13 MHz, DMSO-d_6) δ (ppm): 0.86 (3H, t, $J = 6.4$ Hz, CH$_2$C*H*$_3$), 1.20–1.38 (16H, m, (C*H*$_2$)$_8$CH$_3$), 1.65 (3H, s, 2-CCH$_3$), 3.26 (1H, dt, $J = 13.8$, 7.0 Hz, 3-NC*H*H), 3.26 (1H, dt, $J = 13.3$, 7.3 Hz, 3-NCH*H*), 5.40 (1H, br s, OH, change with D_2O), 6.83 (1H, dt, $J = 7.5$, 1.0 Hz, 5-C*H*), 6.95 (1H, dd, $J = 8.3$, 1.5 Hz, 7-C*H*), 6.95 (1H, dd, $J = 7.3$, 1.5 Hz, 4-C*H*), 7.19 (1H, dt, $J = 8.0$, 1.5 Hz, 6-C*H*). ^{13}C NMR (62.90 MHz, DMSO-d_6) δ (ppm): 14.0 (CH$_2$*C*H$_3$), 21.9 (2-C*C*H$_3$), 22.1 (*C*H$_2$CH$_3$), 26.3 (*C*H$_2$CH$_2$CH$_3$), 27.3 (*C*H$_2$(CH$_2$)$_2$CH$_3$), 28.7 (*C*H$_2$(CH$_2$)$_3$CH$_3$), 28.8 *C*H$_2$(CH$_2$)$_4$CH$_3$), 29.0 (*C*H$_2$*C*H$_2$(CH$_2$)$_5$CH$_3$), 31.3*C*H$_2$(CH$_2$)$_7$CH$_3$), 46.9 (3-N*C*H$_2$), 116.6 (7-*C*H), 119.5 (5-*C*H), 128.9 (6-*C*H), 129.7 (3a-*C*), 129.8 (4-*C*H), 153.2 (7a-*C*), 169.3 (2-*C*). HR FAB-MS: 292.2274 (M^+, $C_{18}H_{30}NO_2$); calcd 292.2277.