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Ionic liquid crystals as alignment medium to measure residual dipolar couplings for carbohydrates

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ABSTRACT

Ionic liquids consisting of *N*-dodecyl-*N*-methyl pyrrolidinium bromide [C_{12}MPB] in a mixture with D2O, decanol, and DMSO were for the first time found to give anisotropic molecular alignment in magnetic fields and are useful to measure residual dipolar couplings (RDCs) from polar analytes, for example, glucose. The system shows less quadrupolar splitting of the deuterated solvent signal compared with other liquid crystal systems and hence less undesired line broadening.

1. Introduction

Residual dipolar couplings (RDCs) are essential parameters in structural determination of organic biomolecules through NMR Spectroscopy. These RDCs are proving to be very powerful for the constitutional, configurational, and conformational analysis of small molecules.[1] Before RDCs, in addition to the chemical shifts and scalar couplings, the determination of the three-dimensional structure of organic molecules by NMR spectroscopy usually involved the measurement of NOEs[2,3] and cross-correlated relaxation[4] to obtain information about dihedral angles, distances, and projection angles, respectively.[5] However these NMR parameters provide only localized structural information and they fail to provide the relative configuration of remotely located molecular fragments.[6]

RDCs can enable the assignment of relative configuration in addition to the NOE due to their r^{-3} dependence. In solid state dipolar couplings are in the kHz range, in solution state they are averaged to zero. By partially orienting the corresponding analytes in the magnetic field residual dipolar couplings are observed. To force the molecules to adapt a minor degree of orientation an anisotropic medium is required.[7]

The size of the dipolar couplings can be reduced by using an orienting medium that induces a low degree of order (order parameter $S < 10^{-3}$). By inducing a low degree of order the anisotropic NMR parameters are significantly averaged, but not entirely. The size of the dipolar coupling is reduced tremendously, such that dipolar couplings are usually smaller than scalar couplings and the spectral quality of high-resolution NMR spectra is retained.

For water soluble biomolecules, liquid crystals,[8] bicelles,[9] micelles,[10,11] bacteria phages,[12,13] and paramagnetic lanthanide tags[14,15] have been developed as anisotropic media to induce the magnetic orientation. Small organic molecules are usually dissolved in organic solvents and hence, for using the alignment approach, it is necessary to find a liquid crystalline alignment medium based on an organic solvent.[16] Stretched polymer gels,[17] liquid crystals such as Poly-γ-benzyl-L/D-glutamate (PBLG/PBDG),[18,19] Poly-γ-ethyl-L/D-glutamate (PELG/PEDG),[20,21] Polyisocyanides,[22] and Polyacetylenes[23] have been developed as alignment media for non polar organic molecules. For polar organic molecules, stretched polymer gels such as cross-linked poly(vinylacetate),[24] cross-linked poly(acrylamide),[25] cross-linked poly(acrylonitrile),[26] and lyotropic liquid crystalline phases of mixtures of $C_{12}E_5$/*n*-hexanol in mixtures of DMSO/D_2O (1:1)[16] were developed as alignment media.

Sample preparation to measure RDCs in stretched polymer gels will take 2–8 weeks depending on the suitable anisotropic medium. Polystyrene gels need up to 4 weeks, based on our experience with these gels. Cross linked PBLG gels need 1–2 months to equilibrate the polymer sticks and 7–10 days for sample diffusion.[27] Poly(dimethylsiloxane) gels are reported to need 12 days to equilibrate the polymer sticks.[28] In the system described below no incubation time is needed.

Extraction of RDCs in liquid crystal alignment media happens to be complicated, due to the relatively large degree of orientation in these media and since the systems become unaligned below a certain LC concentration.[29–31] Here we study another liquid crystal

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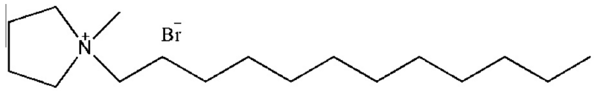


Figure 1. *N*-Dodecyl-*N*-methyl pyrrolidinium bromide [C_{12}MPB].

alignment medium based on the C_{12}MPB ionic liquid crystal in D_2O/DMSO (1:1) mixtures.

As an extension of our previous work, we present here NMR investigations of an ionic liquid medium based on a combination of the *N*-dodecyl-*N*-methylpyrrolidinium bromide [C_{12}MPB]/*n*-decanol with a mixture of water (D_2O) and dimethyl sulfoxide (DMSO-d_6). Although the system does not consist solely of organic solvents, the use of a DMSO/water mixture provides sufficient solvating properties for a class of small polar organic compounds.

Ionic liquid crystals are a fascinating class of molecular materials, both from fundamental and from applied points of view.[32] Due to the ionic nature of these compounds, they form uncommon mesophases like the crystal smectic T phase and the nematic columnar phases.[33–38] Ionic metallomesogens are used as an anisotropic reaction medium for shape-selective synthesis of nanoparticles.[39–41]

Goossens et al.[42] found that *N*-alkyl-*N*-methylpyrrolidinium bromides form a thermotropic crystal smectic T phase at 78–191 °C. Goodchild et al.[43] found that 1-alkyl-3-methylimidazolium halides such as [C_8mim]Cl, [C_8mim]Br, [C_{10}mim]Cl, and [C_{10}mim]Br form lyotropic liquid crystals in 1:1 mixture of H_2O and they performed ^{2}H NMR measurements to confirm the formation of lyotropic mesophases. Shi et al.[44] found that *N*-alkyl-*N*-methylpyrrolidinium bromides such as C_{12}MPB, C_{14}MPB, and C_{16}MPB form lyotropic liquid crystals in 1:1 mixtures of 1-decanol/ water and they confirmed this by polarized optical microscopy (POM) measurements.

Among the *N*-alkyl-*N*-methylpyrrolidinium bromides the *N*-dodecyl-*N*-methyl pyrrolidinium bromide (Fig. 1) was interesting because it forms thermotropic crystal smectic T phases at reasonable temperature (53 °C) and also gave liquid crystals in 1:1 mixtures of 1-decanol/water at 25 °C. Therefore we thought that the *N*-dodecyl-*N*-methylpyrrolidinium bromide could be a useful alignment medium for hydrophilic organic molecules. We also expected that it might be possible to make liquid crystals of *N*-dodecyl-*N*-methylpyrrolidinium bromide in organic solvents because of its dodecyl chain similar to polyisocyanides and polyacetylene polymers, which we had studied earlier.[22,23]

2. Experimental section

The *N*-dodecyl-*N*-methylpyrrolidinium bromide was synthesized[42] in one-step by heating 1-bromododecane and *N*-methylpyrrolidine in dry toluene under an argon atmosphere (Scheme 1). The obtained pale yellow, precipitate was filtered, and recrystallised from methanol/diethyl ether to obtain a white solid.

The NMR meausurements were performed on a Bruker DRX-400 instrument equipped with a BBO gradient probe head. The size of the Fids was 32 K, up to 24,000 sans were used for the ^{13}C gated decoupling spectra on a spectral width of 200 ppm, giving FID resolution of 0.9 Hz. The relaxation delay was 2 s and the 90° pulse duration was 9 µs.

The PALES program uses the mathematical concept of singular value decomposition (SVD) to determine the alignment tensor from a given structure. A crystal structure of glucose[45] (PDB file) and experimental RDCs were used as input files to back calculate RDCs using PALES and described in the paper. For further details and step by step instructions to use PALES, please check the citation[46] which is provided there. An average error of 5% was assumed.

3. Results and discussion

450 mg (75% w/w) of [C_{12}MPB] and 150 mg of D_2O (25% w/w) were directly weighted into an NMR tube and mixed well and allowed to equilibrate overnight. The deuterium quadrupolar splitting for the solvent D_2O signal was found to be 690 Hz for the above sample (Supplementary data, Fig. S1). Then the amount of D_2O was increased to 50%, and the mixture became isotropic.

To enhance the alignment properties of [C_{12}MPB], decanol was used along with solvent D_2O.[45] A 1:1:1 mixture of [C_{12}MPB]/D_2O/decanol (w/w) (33.3% w/w) was weighted into an NMR tube and heated to become homogeneous. Afterward the mixture was cooled back to rt. Then the deuterium quadrupolar splitting for the solvent D_2O signal was found to be 84 Hz (Supplementary data, Fig. S2).

Since [C_{12}MPB] gave liquid crystal alignment in D_2O, we thought that [C_{12}MPB] might give liquid crystal alignment in DMSO also. So we mixed [C_{12}MPB] with DMSO-d_6 (until 70% w/w) to find the deuterium quadrupolar splitting for the solvent DMSO-d_6, but we did not find any quadrupolar splitting for the solvent DMSO-d_6 signal. Then decanol was added to the above [C_{12}MPB]/DMSO-d_6 mixture, but still we did not find any alignment in the magnetic field.

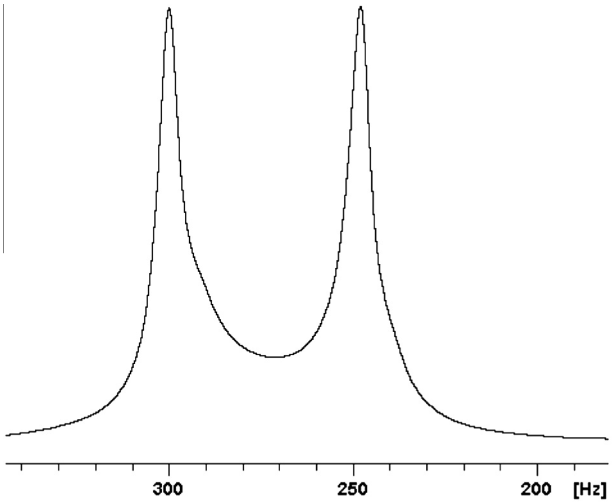
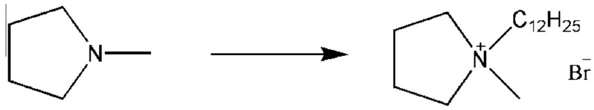


Figure 2. Quadrupolar deuterium splitting of DMSO-d_6 in 1:1:1:1 mixture of [C_{12}MPB]/DMSO-d_6/H_2O/decanol.



Scheme 1. Synthesis of *N*-Dodecyl-*N*-methyl pyrrolidinium bromide [C_{12}MPB].

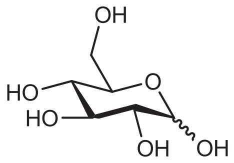


Figure 3. Molecular formula of D-glucose.