Received: 27 January 2022 | Revised: 4 March 2022 | Accepted: 7 March 2022

DOI: 10.1002/mrc.5266

RESEARCH ARTICLE

WILEY

A supramolecular and liquid crystalline water-based alignment medium based on azobenzene-substituted 1,3,5-benzenetricarboxamides

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Funding information
Deutsche Forschungsgemeinschaft, Grant/Award Number: TH1115/11-1

Abstract

A supramolecular, lyotropic liquid crystalline alignment medium based on an azobenzene-containing 1,3,5-benzenetricarboxamide (BTA) building block is described and investigated. As we demonstrate, this water-based system is suitable for the investigation of various water-soluble analytes and allows for a scaling of alignment strength through variation of temperature. Additionally, alignment is shown to reversibly collapse above a certain temperature, yielding an isotropic solution. This collapse allows for isotropic reference measurements, which are typically needed in addition to those in an anisotropic environment, to be performed using the same sample just by varying the temperature. The medium described thus provides easy access to anisotropic NMR observables and simplifies structure elucidation techniques based thereon.

KEYWORDS

^{2}H, alignment media, BTAs, lyotropic liquid crystals, NMR, RDCs, supramolecular chemistry

1 | INTRODUCTION

Since its introduction in the first half of the 20th century, NMR spectroscopy — particularly in isotropic solution — has become one of the most important analytical methods in chemistry, biochemistry as well as a number of other scientific fields. In recent years, its repertoire of methods has increased in size, due to the discovery of systems,[1–8] that allow for a partial alignment of analytes dissolved therein ('alignment media'). Under such conditions, anisotropic NMR observables can be observed, which are usually unavailable in isotropic solution. These observables — for instance, residual dipolar couplings (RDCs)[1] — can yield additional complementary

information about the three-dimensional structure of a compound investigated (the 'analyte').[3–6] Systems currently utilized for this purpose include lyotropic liquid crystals (LLCs) based on both polymeric and supramolecular building blocks, as well as anisotropically swollen or stretched polymer gels.[2,7,8]

Among the LLC-based systems, supramolecular alignment media based on 1,3,5-benzenetricarboxamides[9] (BTAs) are less known but hold great promises. In solution, these typically C_3-symmetric, discotic building blocks can form long, helical stacks driven by threefold hydrogen bonding and π–π-stacking interactions.[10–13] Their handedness is typically random but can be controlled by the introduction of chiral sidechains[14–17] — even if just a small portion of total BTA molecules possess them.[18–21] At sufficient length, the resulting stacks can give rise to columnar liquid crystalline phases,[22–25] but gels[26–29] are generally more common. It has already been demonstrated that such systems can be used as alignment media and even allow for enantiodifferentiation, if chiral building blocks are employed,[25] but systems utilized for this purpose are — so far — also limited to only non-polar, aprotic solvents ($CDCl_3$, CCl_4) and more importantly non-polar analytes,[25,29] significantly limiting their utilization. Because BTA self-assembly is, however, also well known from polar environments,[23,30–33] we were wondering if anisotropic phases formed under these conditions might be suitable as alignment media as well, which would further amplify the repertoire of water-compatible alignment media available.[1,34–43]

Particularly, our interest fell onto the results originally presented by Wang et al.,[23] describing an LLC based on a BTA with azosulfonic acid sidechains in water (Figure 1, BTA **1a**). Compared with recent work in the field of supramolecular alignment media,[41,42] the main difference is that in contrast to chromonic LLCs, which usually form both a nematic and a hexagonal phase depending on the concentration used,[44,45] for the system used here, only a hexagonal phase is known.[23] If this system could successfully be applied as alignment medium — despite the high viscosity expected for hexagonal phases — it would fundamentally extend the range of application for BTA-based media by enabling measurements also under polar conditions. This could be of interest for investigations focussing on water-soluble organic compounds.[46–49] The azo group present in this BTA structure might further allow for control over phase morphology via its photo-isomerization and the resulting changes in self-assembly behaviour.[50–53] Such control is attractive for the system's use as alignment medium, as it might allow for a light-induced switching between anisotropic and isotropic conditions or different analyte orientations — much sought-after properties.

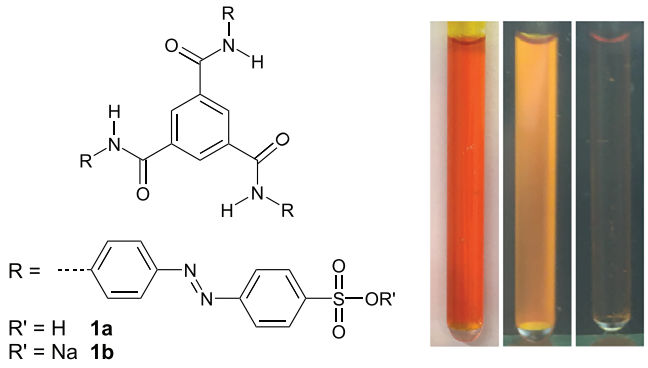


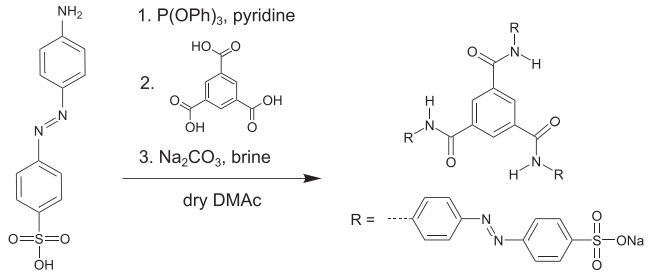
FIGURE 1 Left: General structure of 1,3,5-benzenetricarboxamides (BTAs) and specific compounds investigated originally by Wang et al.[23] (BTA **1a**) and in this work (BTA **1b**). Assuming all-*E* configuration of the azo groups, both of these building blocks are C_3-symmetric. Right: Example of phases obtained under ambient light (left) and between crossed polarizers demonstrating birefringence (middle) compared with a sample at isotropic concentration (non-birefringent, right)

We have therefore synthesized the previously described BTA (more specifically its sodium salt **1b**) and evaluated whether the LLC phase formed by it in aqueous solution is suitable as alignment medium. For this purpose, tests were performed with a selection of analytes of different polarity and bearing different functional groups to study whether the LLC phase is stable in their presence and provides spectra of sufficient quality to allow for the collection of anisotropic NMR observables (compatibility). Additionally, we have also investigated the effects of other additives affecting the pH or ionic strength and of external stimuli (temperature and UV/Vis irradiation) on LLC behaviour to determine whether they allow for control over the medium's alignment properties (stimuli responsivity).

2 | RESULTS AND DISCUSSION

2.1 | Synthesis

Preparation of BTA **1** was carried out essentially according to the original procedure by Wang et al.[23] We only chose to isolate the BTA as the trisodium salt (**1b**; see supporting information [SI]) instead of the protonated species **1a** for ease of purification (Scheme 1).



SCHEME 1 Synthesis of 1,3,5-benzenetricarboxamide **1b** based on the original work of Wang et al.[23] with our modification of isolating the product as trisodium salt. See SI for full experimental details

2.2 | Investigations of liquid crystalline behaviour

2.2.1 | Phase properties and preparation

As a tool for the characterization of critical concentration thresholds, phase homogeneity and effects of additives, we have utilized ^{2}H-NMR and ^{2}H-NMR chemical shift imaging[54]: Homogenously anisotropic, liquid crystalline behaviour is indicated by a splitting of the solvent signal's ^{2}H-NMR resonance line into a doublet (with corresponding solvent signal quadrupolar splitting, $|\Delta\nu_Q|$), which is expected to be constant over the whole sample volume (imaging performed along the sample length, z). As a property dependent on both induced orientation and alignment strength of the solvent, the size of this splitting can serve as a qualitative measure of changes to the mediums microstructure. Under the assumption that the direction of orientation of the solvent is constant, $|\Delta\nu_Q|$ can further be used to investigate effects of changes of temperature[55] and concentration[25,56] on alignment strength of the solvent. We employ this principle here in the liquid crystalline concentration range for samples with and without analyte. These NMR measurements were additionally supplemented with tests for birefringence (see SI).

Our modifications to the original system are twofold: First, we use the sodium salt of BTA **1** instead of its free acid (vide supra); second, D_2O is utilized as solvent instead of H_2O to allow for ^{2}H-NMR measurements. To assess the effects of these differences, we have first investigated a dilution series (0.24 to 0.04 mol-% BTA) analogous to the original experiments performed by Wang et al.[23] In these experiments (see Figure S4), we found a critical concentration of ~0.06 mol-% at 300 K for the isotropic-LLC transition of BTA **1b**, which is considerably lower than the critical concentration of BTA **1a** described previously (0.11 mol-%, room temperature). Between 0.19 and 0.21 mol-% at 300 K, we further detected a sudden jump in solvent signal quadrupolar splitting (by a factor of ~2), which we attribute to the LLC-gel transition reported in the literature (there 0.25 mol-%, room temperature). Note that we inferred the LLC-gel transition from this sudden change of $|\Delta\nu_Q|$, as no noticeable changes to flow behaviour of samples was detected. These were very viscous even at the lowest anisotropic concentrations, probably due to the presence of a hexagonal phase over the entire anisotropic concentration range as also described for the original system based on BTA **1a**.[23] Birefringence also persisted throughout the transition. As both known transitions (isotropic-LLC and LLC-gel) of BTA **1a** are also observed for BTA **1b**, we assume that both systems share a similar behaviour. The differences in transition concentrations are potentially caused by the added sodium ions (for BTA **1b**), as ions were previously shown to affect self-assembly behaviour of charged BTAs.[31,57–59]

2.2.2 | Other solvents, effect of acids, bases, buffers and ions

For a number of other non-polymer-based, water compatible building blocks, for example, graphene oxide (GO)[40,60] and Otting phases,[61] liquid crystalline behaviour is also known in solvents other than water. We thus considered it worthwhile to test for this possibility in the case of **1b** as well. Attempts to produce an LLC phase with other solvents, however, were not successful: DMSO-d_6 yields isotropic solutions even at very high concentrations (tested up to 4.5 mol-%, ~40 wt.-%). In contrast to this, solubility in methanol is already too low (<0.03 mol-%) to allow formation of a liquid crystalline phase, yielding a suspension with only weak colouration of the supernatant liquid. Additional investigations regarding changes of pH further showed that aqueous buffer solutions (in D_2O) are well tolerated (62.5 mM phosphate buffer pH 7 and 1 M Tris buffer pH 8 tested) without noticeable changes to birefringence or changes in observable solvent signal quadrupolar splittings. Addition of inorganic acids and bases (conc./1N HCl, NaOH and KOH) or sodium chloride, on the other hand, resulted in significant disruptions (see SI for further details). An organic sodium salt (sodium cholate) as analyte, however, was tolerated (see below).

2.2.3 | Photoresponsivity

To investigate a possible photoresponsivity of the liquid crystalline phases obtained, we have performed irradiation experiments with dilute solutions and LLC phases of

BTA **1b** (see SI for full experimental details and results). Although UV/Vis spectra in dilute solution clearly indicate a photochemical isomerization upon UV irradiation, this effect was not found to translate into any useful changes to alignment properties (see SI for details) in the LLC state.

2.2.4 | CD spectroscopy

We have further investigated the LLC phase of BTA **1b** in D_2O by circular dichroism (CD) spectroscopy and observed an orientation-dependent CD signature (see SI for spectra and detailed explanation). Because the system is achiral, the presence of a CD signal is not expected. However, for BTA **1a**, a similar observation was made previously by Wang et al.,[23] which was attributed to spontaneous symmetry breaking. In a later publication, the same authors revised their assumption of a symmetry breaking event and attributed the CD signals to measurement artefacts.[24] Based on our own experiments within this study and on another achiral mesogen (disodium cromoglycate [DSCG]),[62] we support this second interpretation of the CD signature being an artefact stemming from the sample's macroscopic anisotropy also for BTA **1b**.

2.3 | Suitability as alignment medium

2.3.1 | Analyte compatibility

To assess the new medium's stability with different types of analytes present, we have chosen a selection of test compounds of different polarities and sizes (Figure 2): (−)-2-Hydroxypinan-3-one (**2**) and (−)-2,3-pinanediol (**3**) feature a comparatively low solubility in water with different amounts and types of hydrogen bonding groups (one donating and two accepting vs. two donating and two accepting groups). Sucrose (**4**) and sodium cholate (**5**) instead possess high solubility in water and are of non-ionic and ionic nature, respectively.

Despite their structural differences, anisotropic samples were obtained with all these analytes, albeit the effects of their addition to the phase differed: With sucrose, only a small reduction of solvent signal quadrupolar splittings compared to the pure, analyte-free phase was observed (∼10%), whereas for all other compounds, the reduction was much more pronounced (>60%). Additionally, a precipitate started to form in these latter cases after about a week (a day for sodium cholate (**5**)), ultimately leading to a collapse of the LLC phase. This did not pose any significant experimental issues, however, as rehomogenization of the sample (by heating; see SI for details) before each measurement session restored their original properties. Still, these observations indicate differences in analyte–medium interactions, which shall be discussed in more detail below.

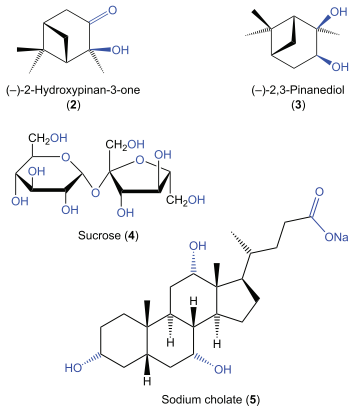


FIGURE 2 Analytes investigated in this study. Polar groups are highlighted in blue

2.3.2 | Spectral quality

In addition to being stable with a given analyte added, an alignment medium must also provide sufficient spectral quality to allow for easy extraction of anisotropic NMR observables. To test whether this is the case for our system, we have performed HSQC-type[63–66] and HECADE[67] experiments (the latter only for sucrose (**4**)) at 300 K. From these, we have extracted $^1H–^{13}C$ total couplings ($\boldsymbol{T}$) of the analytes and calculated their RDCs using the relation $\boldsymbol{D} = (\boldsymbol{T} - \boldsymbol{J})/2$, with scalar couplings ($\boldsymbol{J}$) measured in an isotropic sample of the same analyte in pure solvent. In anisotropic spectra, only very weak or no resonances of the BTA are observable. The only exception is sodium cholate, for which signals of the BTA are of similar magnitude as the analyte's. Due to the structure of the BTA, this poses no problem as signals of the BTA are limited to the aromatic region of the spectrum. A comparison of the *perfect* CLIP-HSQC[66] spectrum of sucrose under isotropic and anisotropic conditions is shown in Figure 3. As can be seen there, the spectral quality is excellent and enables the straightforward extraction of $^1H–^{13}C$ couplings. Also, the alignment strength is comparably low despite the presence of a hexagonal phase, yielding RDCs in the range of several to a few tens of Hz as generally desired in RDC-based structure elucidation.

Interestingly, the fine structure due to additional $^1H–^1H$ couplings observed in the isotropic spectrum is not resolved in the anisotropic spectrum. We attribute this to line broadening effects, possibly due to microscopic inhomogeneities of the LLC phase. For sodium

cholate (**5**) and especially pinanediol (**3**), these effects were particularly strong in measurements at 300 K, complicating coupling extraction in the former case and making the same even impossible in the latter. In an attempt to improve spectral quality, we performed measurements also at higher temperatures (330 K), where analyte alignment strength is expected to be lower due to the reduction of average BTA stack length[10] and increased diffusion. As anticipated, this elevated temperature significantly improved line widths and signal shapes, allowing for facile extraction of couplings. Signals still appeared as doublets without any fine structure, though.

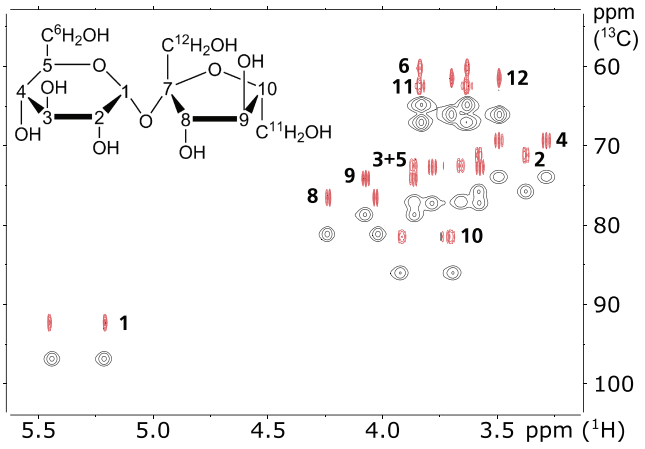


FIGURE 3 Example spectra (*perfect* CLIP-HSQC,[66] 700 MHz proton frequency, 300 K, both in D_2O; see SI for extracted couplings) of sucrose (**4**) in isotropic solution (red, shifted along the indirect dimension for better visibility) and the lyotropic liquid crystal phase formed by 1,3,5-benzenetricarboxamide (BTA) **1b** (black, 0.12 mol-% BTA, sample **81_E**). For a full spectrum, see SI

2.3.3 | Alignment properties

Using the RDCs thus obtained, we were able to calculate reasonable alignment tensors for all analytes using the software RDC@hotFCHT.[68,69] In the case of sucrose, we did so only for the pyranose ring without accounting further for flexibility, as this aspect has already been investigated in great detail elsewhere.[46,70] From these results, a more detailed look into the differences regarding analyte–medium interactions is possible. Specifically, we have utilized the generalized degrees of order (GDOs[71]; Table 1) of the respective tensors for each analyte, which provides a measure for the induced alignment strength of the analyte molecules.

Comparing RDCs and GDOs for 300 and 330 K measurements, a clear reduction of alignment strength is apparent for all analytes — as expected. Closer inspection, however, reveals this reduction to differ significantly in magnitude for sucrose (**4**): Whereas for all other analytes, RDCs and GDOs are reduced significantly (factor of >3), sucrose displays a much more limited response to the temperature changes in terms of RDCs obtained (5.8 vs. 4.7 Hz, max. RDC; see Table 1). Furthermore, sucrose's alignment is surprisingly weak despite the highest solvent alignment (as judged by $|\Delta\nu_Q|$) at both temperatures.

From these results, it seems like interaction strength between analytes and medium, which is connected to alignment strength, differs fundamentally for different compounds: We infer that sucrose exhibits only weak interactions, as changes to solvent signal quadrupolar splittings upon addition are small (vide supra), its alignment induced (RDCs and GDOs) weak and the change in

TABLE 1 Solvent signal quadrupolar splittings ($|\Delta\nu_Q|$) of D_2O, largest residual dipolar couplings (RDCs) and generalized degrees of order (GDOs) from alignment tensor fits using the experimental RDCs for 300 and 330 K measurements (700 MHz proton frequency)

Analyte	*T* (K)	$\lvert\Delta\nu_Q\rvert$ (Hz)[a]	Max. RDC[b]	GDO (*10^{-4})[c]
Hydroxypinanone	300	2.8	11.9	7.4
Pinanediol	300	4.1	26.6[d]	-
Sucrose	300	19.9	5.8	3.8
Sodium cholate	300	9.2	15.9	8.5
Hydroxypinanone	330	<1.0[e]	2.7	1.7
Pinanediol	330	<1.0[e]	9.3	4.9
Sucrose	330	7.6	4.7	-[f]
Sodium cholate	330	<1.0[e]	4.9	2.5

[a]Obtained directly before each measurement.
[b]Absolute value of largest obtained one-bond ^{1}H–^{13}C RDC.
[c]Generalized degree of order (as measure of alignment strength).
[d]Only one ^{1}H–^{13}C RDC (which might not be the largest in this case) was available from proton-coupled 1D ^{13}C NMR.
[e]Splitting smaller than ^{2}H resonance line width.
[f]No long-range RDCs measured at this temperature. See SI for full RDC data.

temperature has only a minor impact. The other three analytes instead exhibit large effects on solvent signal quadrupolar splittings upon addition (vide supra), show strong alignment (RDCs and GDOs) and a pronounced response to temperature changes; we see this as indication for strong interactions between the solutes and the LLC phase. In previous investigations[25,29] with BTA-based media in non-polar solvents, interactions and alignment strength were found to increase with a higher number of hydrogen bonding groups, leading to larger RDCs and increased line broadening. In our present study, a similar correlation of number of hydrogen bonding groups to alignment strength can be observed for analytes with comparable structure and polarity (hydroxypinanone (**2**) and pinanediol (**3**) in Table 1). However, sucrose shows only weak interactions, despite possessing the highest amount of hydrogen bonding groups of all analytes investigated. It thus seems as if hydrogen bonding is not the main factor governing analyte–medium interactions in this case. Instead, analytes possessing *both* highly polar and non-polar groups appear to have the largest effect in this regard.

A possible explanation for this can be found in the mechanism by which BTA molecules self-assemble in water: This process is both generally[9,31] and in this specific case[23] assumed to be driven by hydrophobic interactions between the solvent and non-polar parts of the BTA sidechains. By forming helical assemblies, these non-favourable interactions are minimized, because non-polar groups are sequestered into hydrophobic pockets formed by the BTA core and are thus shielded from the hydrophilic solvent. Additionally, the hydrophilic ends of sidechains (in our case, sulfonate groups) are thought to be located at the outside of the BTA stacks. Presumably, analytes possessing both polar and non-polar groups can weaken these hydrophobic interactions by acting as mediators between the non-polar groups and the polar solvent (akin to amphiphiles). As a result, the tendency of the BTA molecules to self-assemble is reduced in the presence of hydroxypinanone (**2**), pinanediol (**3**) and sodium cholate (**5**), which would explain the reduction of $|\Delta\nu_Q|$ upon addition of these analytes.

2.3.4 | Temperature-induced collapse of LLC phase

Considering the differences in temperature-induced changes between analytes, it seemed worthwhile to have another, closer look at this behaviour. We have thus measured temperature series from 300 to 350 K for sucrose (**4**) and sodium cholate (**5**) (Figure 4) to study these effects in more detail. Once again, the differences in

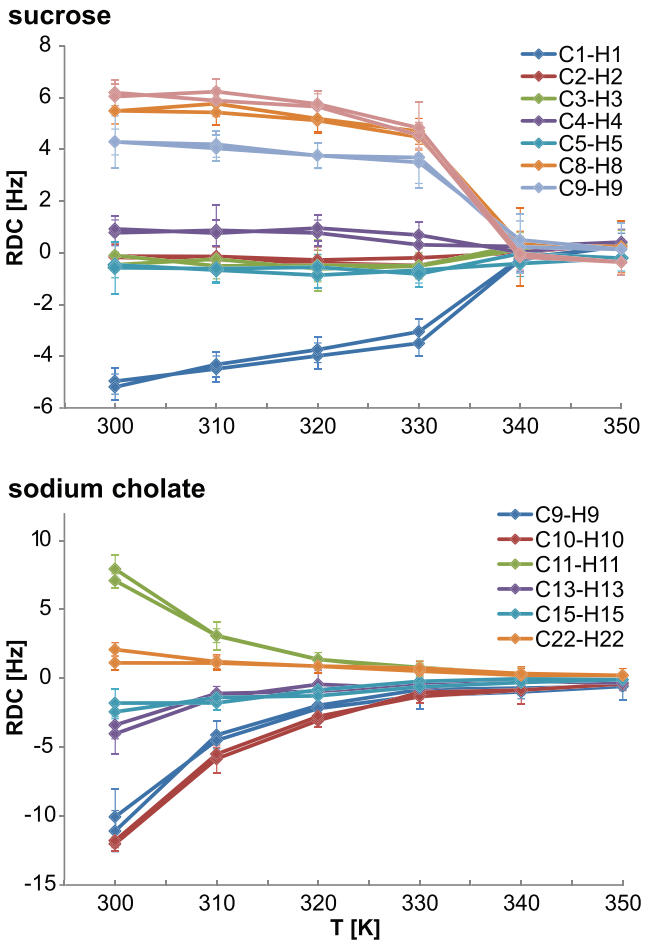


FIGURE 4 $^1D_{C-H}$ residual dipolar couplings (RDCs) from temperature series for sucrose (**4**) and sodium cholate (**5**) (for numbering, see SI) (300 to 350 K and back again, only selected couplings for sodium cholate, both at 600 MHz proton frequency). Slight differences in RDCs displayed compared with Table 1 are reasoned in the usage of different spectrometers (working also at different proton frequencies/magnetic field strengths)

analyte–medium interactions described before are evident: Barely any change is visible for sucrose until the LLC phase begins to collapse above 330 K (indicated by an abrupt change of the RDCs to zero). In contrast, the RDCs decrease steadily with increasing temperature for sodium cholate (**5**) and reach zero above 330 K as well. This behaviour is convenient as it allows fine-tuning of alignment strength for strongly aligning analytes as in the case of pinanediol (**3**). Even more interesting from a practical viewpoint, however, is that for both analytes, the sample reversibly becomes isotropic at a temperature well below the solvents' boiling point. This has allowed us to obtain a set of isotropic couplings (*J*) needed for calculation of RDCs from the *same* sample (referred to as internal reference). This approach has previously been reported for other alignment media, for example, bicelles,[47,72] and more recently chromonic phases.[41,42]

When comparing these values to those obtained from a separate isotropic sample without BTA (named external reference here), differences are smaller than the corresponding uncertainties with only one exception (see SI). Consequently, scalar couplings *J* of the internal reference can alternatively be used (instead of the external reference utilized thus far) to calculate RDCs and in turn the alignment tensor. Furthermore, comparing differences between eigenvectors of tensors calculated from RDC sets with internal and external reference values for *J* also yields only negligible differences (Figure 5, shown here for sodium cholate (**5**)). The same is true for the 5D angle[35,69] calculated between these tensors (the tensor analogue to the cosine between two vectors [ranging from 0° to 90°]; lower degree value equals higher similarity of orientation) with 1.6° for 300 K and 5.6° for 330 K measurements, respectively. Thus, a single sample of the analyte in BTA **1b** solution, measured at two different temperatures, is sufficient for structure elucidation.

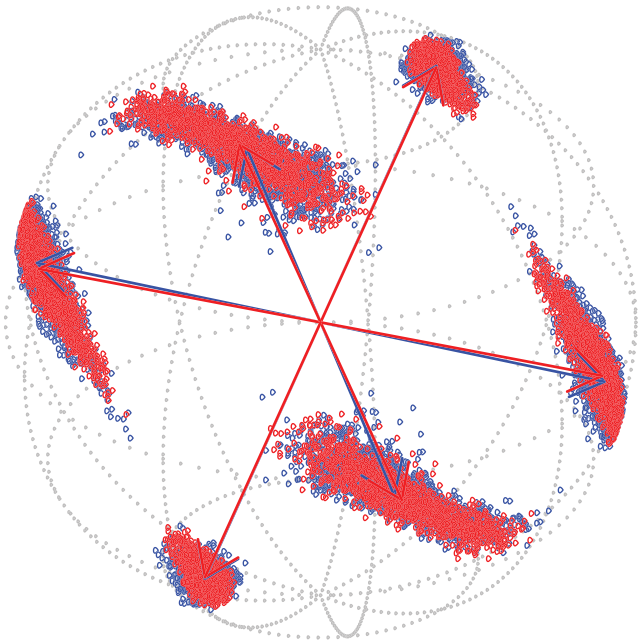


FIGURE 5 Comparison of two sets of alignment tensor eigenvectors obtained using the same set of total couplings (sodium cholate (**5**), 300 K, 700 MHz proton frequency, 0.14 mol-% BTA, 20 mg analyte, sample **1_D**) but different sets of scalar couplings: For the red eigenvectors, scalar couplings are obtained from the same sample at 350 K (internal reference). For the blue eigenvectors, scalar couplings of a separate sample with the analyte in water were used (external reference). Arrows correspond to the best solution obtained in alignment-tensor calculations, whereas scattered points show the distribution of vectors in Monte-Carlo bootstrapping[73] (as a measure of certainty)

3 | CONCLUSION

We have presented a water-compatible and supramolecular alignment medium based on the BTA motif with highly polar, azobenzenesulfonate-bearing sidechains. This alignment medium was successfully utilized to collect ^{1}H–^{13}C RDCs for a selection of analytes from water-soluble terpenes to highly polar sugars or ionic steroids. HSQC and HECADE spectra utilized for this purpose allowed for easy extraction of couplings. Additionally, the alignment strength was found to be scalable by temperature, allowing for control of the RDC's magnitudes up to a point (at 350 K), where the solution becomes isotropic and RDCs vanish. This has allowed us to obtain the isotropic scalar couplings needed for determination of RDCs from the same sample — as opposed to the separate sample without alignment medium usually required for this purpose. The RDC-based structure elucidation process can thus be considerably simplified using this medium.

4 | EXPERIMENTAL

Details concerning experimental procedures, optical spectroscopy measurements, sample preparation and phase tests, as well as extraction of RDCs and their computer-based interpretation are provided in the SI. The data that support the findings of this study are openly available in Zenodo at https://doi.org/10.5281/zenodo.6020399.

ACKNOWLEDGEMENTS

The authors would like to thank Mr. Christian Lorenz for help with preparation of the required BTA, Dr. Volker Schmidts for aid regarding the use of RDC@hotFCHT, Dr. Jonas Kind for assistance with UV/Vis measurements and the mass spectrometry department of the Technical University of Darmstadt for analytical support. We are further grateful to the Deutsche Forschungsgemeinschaft (DFG) for funding (grant TH1115/11-1).

Open access funding enabled and organized by Projekt DEAL.

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How to cite this article: K. Knoll, D. Herold, M. Hirschmann, C. M. Thiele, *Magn Reson Chem* **2022**, *60*(6), 563. https://doi.org/10.1002/mrc.5266