EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: L-Valine derivatised 1,3,5-Benzene-tricarboxamides as Building Blocks for a new Supramolecular Organogel-like Alignment Medium

Authors: Kevin Knoll, Martin Leyendecker, and Christina Thiele

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201801306

Link to VoR: http://dx.doi.org/10.1002/ejoc.201801306

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201801306

WILEY-VCH

L-Valine derivatised 1,3,5-Benzene-tricarboxamides as Building Blocks for a new Supramolecular Organogel-like Alignment Medium

Kevin Knoll,[a] Martin Leyendecker,[a] and Christina M. Thiele*[a]

Abstract: We were previously able to demonstrate that mesogens self-assembled from small molecules, more specifically 1,3,5-benzene-tricarboxamides (BTAs), are capable of forming lyotropic liquid crystalline phases in chloroform and CCl_4, which are suitable for use as alignment media for small organic molecules. In this context, however, it became quickly apparent that one major limitation of such systems arises from the disruption of the self-assembly process by certain analytes. Here, we present a modified version of our original BTA-monomers, containing an additional L-valine moiety. Through this modification, the number of available hydrogen bond acceptors/donators per monomer is doubled, resulting in vastly increased stability. The new system thus obtained exhibits anisotropic properties at much lower concentrations of BTA and allows for the determination of residual dipolar couplings for previously incompatible analytes like isopinocampheol (IPC). Interestingly, the BTA system rather exhibits the properties of an organogel than of a liquid crystal. This is thus the first report of the use of an organogel based alignment medium.

Introduction

In recent years the possibilities of organic structure determination using nuclear magnetic resonance spectroscopy (NMR) have been much expanded thanks to ongoing and intensive research in this field. Special attention has been paid in this regard to the elucidation of the three-dimensional structure of compounds. Maybe one of the most successful new techniques in this context is the structure determination using residual dipolar couplings (RDCs):[1] Here the direct through-space interactions of two nuclear spins are utilized to obtain not only distance, but also orientational correlations, adding to the information acquired through Nuclear Overhauser Effect (NOE)[2] and Karplus[3] relations.

In order to obtain RDCs special experimental requirements must be fulfilled, owing to the fact, that dipolar couplings are anisotropic interactions.[4] As such they are strongly dependent on the orientation of the spin-spin-vector in relation to the external magnetic field B_0, which makes them non-observable in the isotropic solutions normally used in NMR-spectroscopy. This is due to the rapid, unrestricted tumbling of the molecules and the corresponding averaging of anisotropic interactions to zero. Thus RDCs are generally measured in lyotropic liquid crystals or anisotropically swollen gels - collectively called alignment media - Here, the free tumbling of the molecules is restricted by the presence of mesogens or gel pores/cavities and therefore some orientations are favoured over others, which results in partial alignment. This alignment induced is ideally rather small, so that only a small fraction of the dipolar coupling (hence called residual dipolar coupling), approximately on the same order of magnitude as the scalar coupling, remains and spectra thus stay easy to interpret. This last point, specifically, is of major importance; in fact did structure determination using dipolar couplings, while in principle known for several decades,[5] only become feasible for all but the simplest molecules with the advent of weak aligning media in the 1990s.[6]

From this, it is immediately apparent, that the availability of suitable alignment media, both in relation to the induced degree of order and compatibility with different solvents, analytes and measurement conditions is of critical importance to the application and further development of RDC based methods in organic structure determination. Furthermore these media should be easily obtainable, modifiable and allow for the highest possible ease of sample preparation.

Currently, the two most common groups of alignment media used for organic compounds are lyotropic liquid crystals (LLC) and anisotropically swollen gels. While there are few liquid crystalline alignment media based on small molecule mesogens[7] and peptidic LLC phases for water[8] and MeOH,[9] the alignment media compatible with organic solvents thus usually involve either macromolecular mesogens[10] or covalently cross-linked polymer gels[11]. However, to the best of our knowledge no (low molecular weight) organogelator has been successfully applied for this purpose yet as these are – in contrast to covalently crosslinked polymer gels – cross-linked/self-assembled via hydrogen bonds or via van der Waals forces,[12] which usually do not sustain the strain needed for alignment. The polymeric nature of the most-commonly applied alignment media thus usually asks for a certain synthetic effort involving preparation of highly pure monomers under strictly inert conditions[10e, 10k]. Preparation of anisotropically swollen gels on the other hand may involve uncommon equipment[11e, 11g, 11l] or long equilibration times in sample preparation[11c, 13]. Sample preparation times for some of the gels can be significantly reduced by a compressing/ stretching-apparatus.[11h, 13a, 14] Both of these groups have additionally in common, that the (alignment-) properties of the final product can depend on the chosen polymerization and/or crosslinking conditions. This can give rise to challenges associated with reproducibility, since

[a] K. Knoll, M. Leyendecker, Prof. Dr. C. M. Thiele
Technische Universität Darmstadt,
Clemens Schöpf Institut für Organische Chemie und Biochemie,
Alarich-Weiss-Str. 4, 64287 Darmstadt, Germany.
*E-Mail: cthiele@thielelab.de; Homepage: www.thielelab.de
Supporting information for this article is given via a link at the end of the document

even small differences can impact polymer properties like chain length or degree of crosslinking and in turn alignment properties.[15]

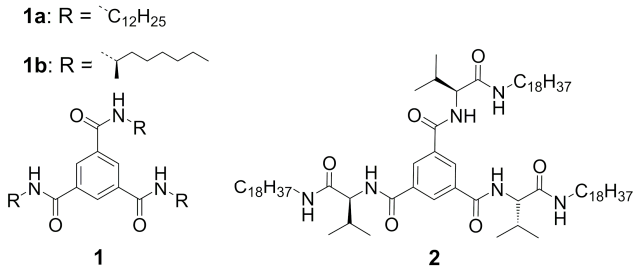


Figure 1: The previously reported BTA monomers[16] with long aliphatic sidechains (**1**; a: achiral, b: chiral side chain) and the modified structure with additional L-valine moieties inserted between aromatic core and aliphatic chain (**2**). This simple modification doubles the amount of hydrogen bond acceptors/donators and thus allows for stronger interactions between monomers.

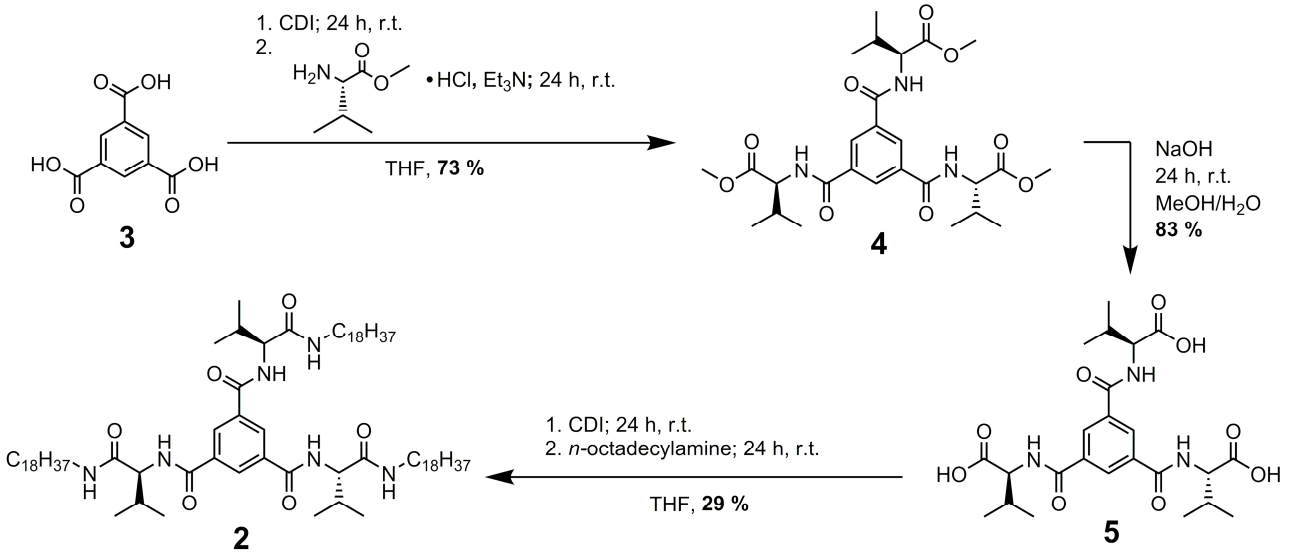
An answer to these polymer-related challenges might be the use of non-polymeric alignment media build from small molecules.[7] In this context we were recently able to demonstrate that mesogens self-assembled from small molecules using non covalent interactions, so called supramolecular polymers, can be used to obtain suitable alignment media in organic solvents as well.[16] For this purpose we have utilized benzene-tricarboxamides (BTAs, **Fig. 1**), known to self-assemble into long helical stacks by threefold hydrogen bonding in solution.[17] These aggregates can then in turn act as mesogens essentially analogous to the polymer helices in conventionally used polymer-based alignment media. Additionally it is possible to obtain chiral BTA stacks and control the handedness of the supramolecular helix[17b] by adding a stereocenter to the substituents and thus causing one helix sense to be energetically[18] favoured over the other.[19] Due to diastereomorphous interactions between chiral mesogens and chiral analyte, leading to different orientations of the latter depending on configuration,[10b] such a chiral alignment medium enables discrimination of enantiomers based on anisotropic NMR observables.[10c, 10d, 10j] As we were able to demonstrate,[16] this principle remains operative even if just a small amount of chiral BTA (**1b**) is added to the bulk of achiral BTAs (**1a**, sergeant-and-soldier-principle[20]).
In addition to the aforementioned lyotropic liquid crystalline phases, there have also been reported some cases, in which BTAs form hydro-[21] and organogels,[22] either by polymer-analogous coiling of long aggregates[22b, 23] and/or extensive cross-linking[22a] between monomers.

A large advantage of such supramolecular systems lies not only in the much easier preparation and purification of the monomers required, but also in the absence of a preceding polymerization step, avoiding the influence of aforementioned polymer-specific factors. A considerable limitation of our previously reported systems stems, however, from the fact that supramolecular polymers are dynamic systems and therefore vulnerable to disturbances: Other components of the sample, most prominently the analyte can interfere with this self-assembly, disrupting the alignment properties.[16] In our case even the presence of the single hydrogen bond donor/acceptor in isopinocampheol (IPC) caused a significant drop in quality of the spectra obtained, making the extraction of RDCs impossible. It became therefore evident, that the basic BTA structure needed to be modified in order to increase the supramolecular stacks' stability and in turn reduce the influence of other sample components on self-assembly.
For this purpose we have synthesized a BTA with an additional L-valine moiety inserted between aromatic core and the aliphatic chain (**2**). Our hypothesis is, that this modification effectively doubles the amount of possible hydrogen bonds between monomers and thus should considerably increase the stability of the resulting stacks. Alignment media obtained this way are therefore expected to be much more tolerant towards analytes or solvents capable of disrupting monomer self-assembly. Additionally, the amino acid moiety provides easy access to a stereogenic center, and therefore potential enantiodifferentiating properties. As several groups[24] have demonstrated, the supramolecular interactions of such amino acid containing BTAs can also be easily tuned by the choice of amino acid and should thus facilitate further customizations in the future. In the following we thus investigate the alignment properties of the L-valine-modified benzene-tricarboxamide obtained.

Results and Discussion

Synthesis

The desired tris-L-valine-*n*-octadecyl-BTA was synthesized using a three step sequence starting form 1,3,5-benzene-tricarboxylic acid (**3**, Scheme 1), using carbonyldiimidazole (CDI) as coupling reagent.[25] An intermediate protection of the amino acid moiety as ester is required to avoid oligomerization reactions during the first step. We have chosen this CDI based coupling method over the, especially in regards to BTAs, more commonly used route[22b, 26] utilizing carboxylic acid chlorides in order to avoid a possible racemization of the amino acid , which is expected to occur when such rather harsh reaction conditions are used.[25]
Using this sequence the L-valine-methyl-ester-BTA (**4**) was obtained in 72.7 %, the BTA-amino acid (**5**) in 83.0 % and finally the target compound (**2**) in 28.9 % yield, respectively. For the last step it is of great importance to use a substoichiometric amount of CDI and to make sure that all of it has reacted prior to adding the amine (e.g. through ^{1}H NMR). Otherwise a side product (a substituted urea) would form (presumably) from the reaction of surplus CDI with some of the amine, which we found to be essentially inseparable from **2**. The final product is a white (if very pure) to off-white solid, essentially insoluble in most polar solvents (except for trifluoroacetic acid) and very sparsely soluble in non-polar solvents. This made purification challenging, but we found a solid-liquid extraction using 2-propanol as the liquid phase to be quite effective.



Scheme 1: Three step synthesis of the tris-L-valine-*n*-octadecyl-BTA (**2**) from 1,3,5-benzene-tricarboxylic acid: 1,3,5-benzene-tricarboxylic acid (**3**) is coupled with L-valine methyl ester using CDI. The resulting BTA-valine methyl ester (**4**) is then deprotected by saponification and the BTA-amino acid (**5**) obtained subsequently coupled utilizing CDI once again, this time with *n*-octadecylamine, forming the target BTA (**2**). This reaction sequence should, in theory, allow for the synthesis of similar BTAs containing different amino acids as well.

General Properties of Phases

Before describing our new system´s interactions with selected analytes it is necessary to first discuss some general properties, as there are a number of major differences compared to our original systems.
For the previously described, purely alkyl substituted BTAs, sample preparation consists simply of homogeneously dissolving the BTA monomers in the solvent by heating. This method was, however, rather unsuccessful for our new system and yielded mostly isotropic samples or if anisotropy was observed at all it was badly reproducible. Further investigation (for more details see SI section 2) then revealed a number of factors impacting phase behaviour decisively. These, were not observed for the original system:

- High temperature and centrifugation seem to heavily disrupt aggregation. This is clearly demonstrated by the fact, that even previously anisotropic samples became irreversibly isotropic upon centrifugation or heating close to boiling point of the solvent. (This allows to obtain both isotropic and anisoptropic couplings from the same sample, see SI sections 2 and 6.5)

- Magnetic fields appear to play a major role: Samples prepared without the presence of the spectrometer´s B_0 field stayed isotropic in all cases.

- The viscosity of the sample at the time of entering the magnetic field is another point of critical importance. While all samples prepared formed a solid gel after some time, those which had already partly congealed exhibited drastically reduced ^2H solvent signal quadrupolar splittings (as indicator of anisotropy and strength thereof) or were even isotropic.

- Finally we did also oberserve some effect of the purity of the used deuterated solvent, with freshly destilled $CDCl_3$ (acid and water free) yielding best results in terms of solvent signal quadrupolar splittings.

Based on these findings we were able to devise an optimized preparation procedure: The phase components are mixed by gentle shaking, then directly placed in the pre-heated spectrometer (320 K) while the mixture is still fluid and kept inside the field until the solvent signal quadrupolar splitting is stable (approx. 3 h). Phases thus obtained appear as homogenous, slightly turbid gels. Surprisingly, there was no observable birerefringence between crossed polarizers.
The approximate concentration range for anisotropic behaviour in deuterated chloroform lies between 0.7 and 4.0 percent (w/w), which is a significant improvement over the original system with 26 to 33 percent (w/w)[16a]. Even higher concentrations than that may be possible, but mixing the phase components becomes increasingly difficult above 4 percent w/w), because of their high viscosity, leading to highly inhomogeneous phases unsuitable for determination of RDCs. Also, our new system does not seem to possess a lower critical concentration, at which it starts to become partly isotropic. Instead it steadily progresses towards lower solvent signal quadrupolar splittings with decreasing concentration, eventually reaching a point, at which the individual branches of the ^2H signal are no longer distinguishable. With values of up to 200 Hz the solvent signal quadrupolar splittings of our new system are significantly lower than for the purely alkyl substituted BTAs (>1000 Hz). Still, taking into account the vast differences in solubility, this might just reflect the difference in monomer concentration.

The in some cases significant differences between our original, purely alkyl substituted and the new, amino-alkyl substituted BTA, especially in regards to the successful preparation of anisotropic samples, certainly urge the question, in how far the valine moiety changes the self-assembly process. In fact, considering the apparent lack of typical liquid crystalline properties (fluidity, birefringence) and of a lower critical concentration typically observed for liquid crystalline alignment media, it must be questioned, whether our new system is a liquid crystal at all. Actually, it seems to have far more in common with a gel. It would then, however, differ significantly from other (covalently cross-linked) gel based alignment media, for which external strain is required to induce anisotropic properties.

Returning to the question regarding what causes this transition from lyotropic liquid crystal to gel, the most obvious explanation is the additional set of hydrogen bond donators/acceptors present in our new monomer. While this was intended to predominantly enhance the supramolecular stacks´ stability, it of course also allows for cross-linking between monomers or aggregates. Compared to the set of hydrogen bond donators/acceptors at the BTA core, the outer set of hydrogen bond donators/ acceptors has much more degrees of freedom. This probably promotes cross-linking. The sensibility of our system to heating and centrifugation is then likely caused by the destruction of already present aggregates, followed by cross-linking of the liberated monomers/oligomers. The result is a heavily cross-linked state, from which the system cannot recover, because doing so would require an extensive micro-scale reorganisation. Still, some moderate heating seems to be beneficial, possibly because this allows for faster reorientation of stacks and/or promotes certain self-assembly processes

Since all samples became gels after some time, the aforementioned cross-linking can apparently not be suppressed completely. That we are able to obtain anisotropic phases at all, is then probably owed to the orientation of preformed stacks being faster than cross-linking. If these small aggregates are subjected to a strong directing force, in our case a magnetic field, the resulting gel then contains small, uniformly oriented, anisotropic cavities, which in turn allow for alignment of analytes. Such an interaction between the aggregates and the magnetic field is plausible, as BTA stacks are known to possess a macro dipole moment along the stack axis[27] and orientation in a magnetic field has previoisly been reported for different supramolecular systems other than BTAs.[28]

Experiments with an analyte lacking hydrogen bond acceptors/donators: *β-pinene*

Before adding an analyte potentially capable of disrupting BTA-self-assembly to our system, we have first performed tests with two enantiomers of an analyte devoid of hydrogen bond acceptors/donators at two different temperatures (300 K and 320 K). This was done both in order to investigate general phase properties like stability, alignment strength and enantiodifferentiation without interferences and to provide a point of reference in terms of relative stability. The analyte chosen for this purpose was β-pinene (**Fig. 2**), whose influence on BTA self-assembly we found to be minimal in our previous work.[16]

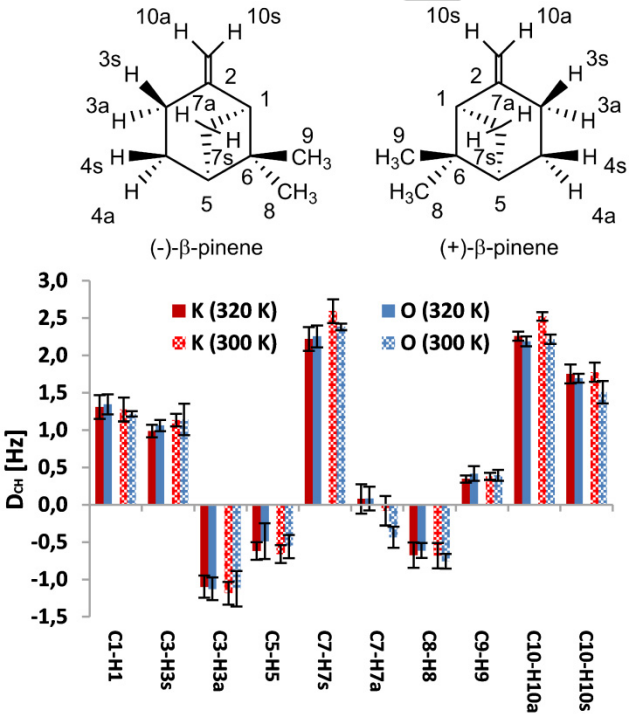


Figure 2: Extracted one-bond C-H-RDCs for samples "K" with (-)- and "O" with (+)-β-pinene, containing 4.0% BTA **2** (w/w, see SI section 3.2 for exact sample compositions). Solvent signal quadrupolar splittings: ($\Delta\nu_Q$ (300/320 K) = 129.88/125.55 Hz ("K"), 129.47/125.38 Hz ("O")).

Samples with β-pinene exhibit very similar solvent signal quadrupolar splittings to those prepared without any analyte. While the RDCs observed (Fig. 2B) amount only to a few Hz, probably due to the relatively small alignment strength, fits[29] performed using these datasets yielded very good Q-factors[30] for both temperatures. There seems to be no enantiodifferentiation present, however, as RDCs for the different enantiomers are essentially identical within the estimated error. This is in contrast to our original, purely alkyl-substituted BTAs, in which a stereogenic center, even within a small fraction of monomers used, was able to make enantiomers distinguishable.

Experiments with an analyte containing hydrogen bond acceptors/donators: Isopinocampheol

With our original, purely alkyl-substituted BTAs it was difficult to obtain stable, anisotropic phases, when isopinocampheol (IPC, **Fig. 3**), an analyte containing just a single hydroxy group was added.[16] Since such a group can act both as a hydrogen bond acceptor and donor, it is expected to be able to disrupt proper self-assembly of the stacks. After the promising results with β-pinene we therefore repeated the experiments described in the previous section with IPC as analyte.

The effects of adding IPC to our new system were very limited and did not significantly differ from those obtained with β-pinene. While sample components formed a gel slightly faster, probably because the additional functional group on the analyte promotes cross-linking to some degree, this poses no problem if the samples are properly prepared. Changes in the solvent signal quadrupolar splittings observed in comparison to the pure phase here again amounted to just a few Hz and spectral quality was still good at 320 K, even though lines were broader and line shape distortions appeared. At 300 K, on the other hand, distortions and line broadening became very pronounced for some signals, making extraction very difficult from CLIP-HSQCs[31] and necessitating the use of F1 coupled HSQC[32] spectra for determination. Surprisingly, we found the average size of the RDCs obtained to be more than an order of magnitude larger than for β-pinene, which could also be an explanation for the observed reduction in spectral quality. Nevertheless, this is a stunning observation, as it could mean, that the size of observable RDCs is, at least for such BTA based systems, heavily dependent and therefore tuneable by specific monomer-analyte interactions.

We were able to extract all C-H-couplings (**Fig. 3**) from our spectra measured at 320 K and most from those measured at 300 K. The missing RDCs (C4-H4s and C5-H5) were unobtainable due to strong signal distortions, likely due to too strong alignment. Accordingly distortions decreased substantially at even slightly reduced BTA concentrations (3.5% ("S") vs. 4.0%, both w/w; see SI section 3.2) and the aforementioned couplings became extractable even at 300 K.

Fits performed with these RDC datasets as before yield excellent Q-factors, again with better results for the 320 K measurements. Regardless of the greater size of the RDCs, however, the differences in couplings between enantiomers were still small. Only a few are greater than the estimated range of error. It is therefore not possible to answer the question regarding enantiodifferentiation at this point; still, even if there was such an effect, it seems to be very limited in our system. A possible explanation for this lack of enantiodifferentiating properties could be the gel-like nature of our system, which most likely is accompanied by a more complex micro structure, deviating from the ideal 6-fold hydrogen bonding. In such a situation, the stereogenic information of the stereogenic centre of the amino acid might not be properly translated into a preferred helical sense. Furthermore the long alkyl chains (C_{18}) could shield the stacks´ centre too much and thus prohibit the proper interaction necessary for enantiodiscrimination. In order to check for the latter we have also synthesised the *n*-dodecyl-analogue of BTA **2** - While this compound also formed gels, none of them demonstrated anisotropic behaviour, however.

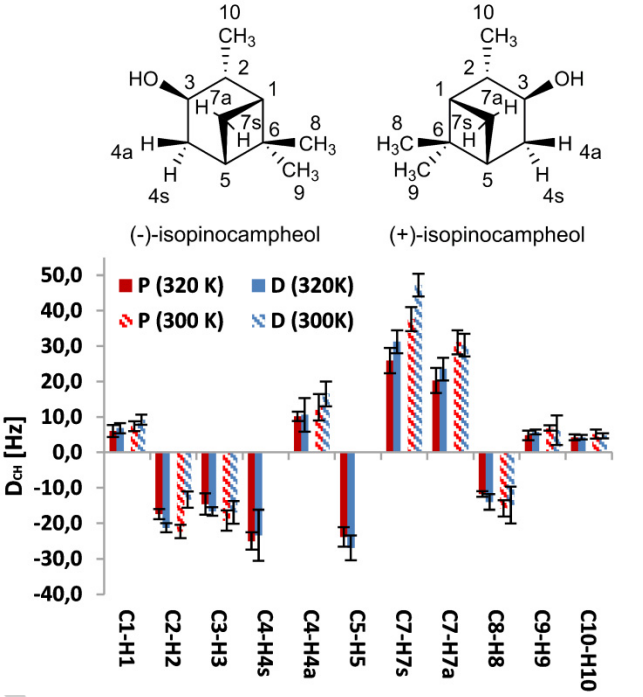


Figure 3: Extracted one-bond C-H-RDCs for samples "P" with (-)- and "D" with (+)-IPC, containing 4.0 % BTA **2** (w/w, see SI section 3.2 for exact sample compositions). Values (RDC and errors) for sample "P" were scaled up according to the difference in solvent signal ^{2}H quadrupolar splitting for comparison ($\Delta\nu_Q$ (300/320 K) = 128.23/126.51 Hz ("D"), 121.85/114.29 Hz ("P")).

Conclusions

We were able to demonstrate that the stability of BTA-based supramolecular alignment media against self-assembly disrupting analytes can be decisively improved by increasing the amount of hydrogen bond donors/ acceptors via the addition of an L-valine moiety. While this addition apparently leads to unwanted cross-linking between monomers, proper sample preparation can minimize the impact of these interactions. The spectrum of compatible analytes for these systems is therefore vastly increased. In tandem with our observation that alignment strength for a given analyte is apparently depending on specific monomer-analyte interactions, this could in future allow to tailor BTA-based alignment media in $CDCl_3$. Probably the only setback is the apparent loss of enantiodifferentiating properties compared to our originally published sergeant-and-soldier systems. As this is, however, likely caused by the additional set of hydrogen bond acceptors changing the way stacks are formed from the simple three-fold helical stacking mode to a more complex one, suitable changes to the BTA structure might be able to amend this as well.

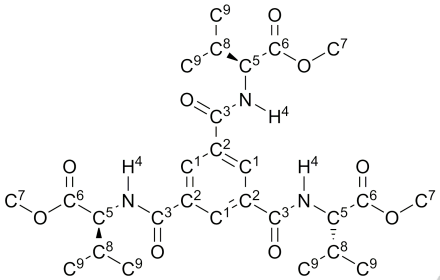
While a determination of the exact phase morphology is certainly beyond the scope of this work, we can at least attest, that our new system shares more characteristics with a gel than it does with a liquid crystal. If it should indeed prove to belong in the

former group, this would represent an entirely new class of amorphous supramolecular organogel-based alignment media.

Experimental Section

Synthesis of
N^1,N^3,N^5-tris-[L-Val-OMe]-benzene-1,3,5-tricarboxamide (4)

In a flask flushed with argon 1.11 g trimesic acid (5.28 mmol, 1 eq.) were dissolved in 100 ml of dry THF. This solution was then cooled to 0 °C, 2.67 g CDI (16.47 mmol, 3.1 eq.) were added slowly and the resulting mixture stirred for 24 h at room temperature. Next, the mixture was cooled to 0 °C again, 2.92 g L-valine methyl ester hydrochloride (17.42 mmol, 3.3 eq.) and 2.6 ml triethylamine (1.89 g, 18.71, 3.5 eq.) added and the stirring continued for another 24 h at room temperature. Finally, the solvent was removed *in vacuo* and the residue recrystallized from 2-propanol, yielding 2.11 g (3.84 mmol, 72.7 %) of a white, voluminous solid. This is in principle the procedure used by Gelinsky et al.[33] to obtain substituted BTAs. This compound has previously been prepared by Ishioka et al.[22b]



^{1}H NMR (500 MHz, $CDCl_3$, 300 K, ref.: $CDCl_3$ = 7.24 ppm): δ = 8.38 (s, $3H^1$), 6.97 (d, J = 8.6 Hz, $3H^4$), 4.76 (dd, J = 8.6, 5.3 Hz, $3H^5$), 3.78 (s, $9H^7$), 2.27 (m [expected: dqq], $3H^8$), 1.01 (d, 4.0 Hz, $9H^{9a}$), 0.99 (d, 4.0 Hz, $9H^{9b}$) ppm.

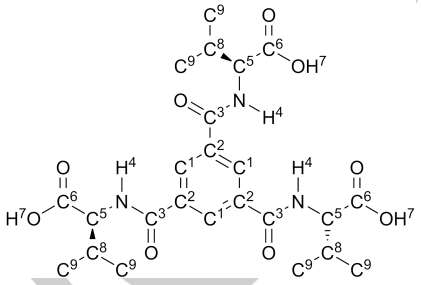
^{13}C NMR (126 MHz, $CDCl_3$, 300 K, ref.: $CDCl_3$ = 77.21 ppm): δ = 172.52 (C^6), 165.75 (C^3), 135.08 (C^2), 128.85 (C^1), 58.16 (C^5), 52.58 (C^7), 31.72 (C^8), 19.28 (C^{9a}), 18.35 (C^{9b}) ppm.

MS (ESI): expected: 550.28 m/z; found: 550.28 m/z.

IR (pure solid, characteristic bands): ν_{N-H} = 3222.13 (valence), ν_{Ar-H} = 3056.08 (valence), ν_{-CH3} = 2958.53 (valence), $\nu_{C=O}$ = 1754.31 (valence, ester), $\nu_{C=O}$ = 1640.92 (valence, amide), ν_{N-H} = 1551.84 (deformation) cm^{-1}.

Synthesis of
N^1,N^3,N^5-tris[L-Val-OH]benzene-1,3,5-tricarboxamide (5)

To a suspension of 2.11 g of the N1,N3,N5-tris-[L-Val-OMe]-benzene-1,3,5-tricarboxamide (3.84 mmol, 1 eq.) in 200 ml of THF were added 768 mg of sodium hydroxide (19.20 mmol, 5 eq.) dissolved in 100 ml methanol and 50 ml deionised water and the resulting mixture then stirred at room temperature for 24 h. The suspension obtained was brought close to neutral with 1N HCl (approx. 90% of the theoretical amount) and the solvents were subsequently removed *in vacuo*. This residue was then dissolved in 50 ml of deionised water and acidified with 1N HCl (pH = 2) causing a white solid to precipitate, which was collected by filtration and dried thoroughly *in vacuo*. Yield: 1.62 g of a yellowish solid (3.19 mmol, 83.0 %). This is essentially the general procedure proposed by Theodorou et al.[34]. This compound has previously been prepared by Ishioka et al.[22b]



^{1}H NMR (500 MHz, DMSO-d_6, 300K, ref.: DMSO = 2.5 ppm): δ = 12.67 (s, $3H^7$), 8.74 (d, J = 8.2 Hz, $3H^4$), 8.40 (s, $3H^1$), 4.33 (m, $3H^5$), 2.21 (pseudo sx [expected: dqq], J = 6.8 Hz, $3H^8$), 0.99 (pseudo-t [expected: 2*d], J = 6.1 Hz, $18H^{9a+b}$) ppm.

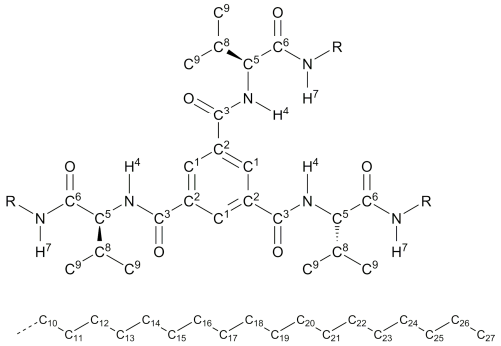
^{13}C NMR (126 MHz, DMSO-d_6, 300K, ref.: DMSO = 39.51 ppm): δ = 172.98 (C^6), 166.42 (C^3), 134.52 (C^2), 129.56 (C^1), 58.56 (C^5), 29.58 (C^8), 19.35 (C^{9a}), 18.82 (C^{9b}) ppm.

MS (ESI, DMSO): expected: 508.23 m/z; found: 508.23 m/z, 586.25 m/z (M+DMSO).

IR (pure solid, characteristic bands): ν_{N-H} = 3226.33 (valence), ν_{Ar-H} = 3057.23 (valence), ν_{-CH3} = 2966.57 (valence), $\nu_{C=O}$ = 1716.18 (valence, acid), $\nu_{C=O}$ = 1634.22 (valence, amide), ν_{N-H} = 1546.29 (deformation) cm^{-1}.

Synthesis of
N^1,N^3,N^5-tris-[L-Val-*n*-octadecyl]-benzene-1,3,5-tricarboxamide (2, BTA-Val-C_{18})

In a flask flushed with argon 806.00 mg of the N1,N3,N5-tris-[L-Val-OH]-1,3,5-benzene-tricarboxamide **5** (1.59 mmol, 1 eq.) were suspended in 70 ml of dry THF. This suspension was then cooled to 0 °C, 757 mg of CDI (4.67 mmol, 2.9 eq.) were added and the resulting mixture stirred for 24 h at room temperature. Afterwards it was once again cooled to 0 °C, 1.465 g *n*-octadecylamine (5.44 mmol, 3.4 eq.) dissolved in 60 ml of dry THF were added slowly via dropping funnel and then stirred for another 24 h at room temperature. The resulting solid was collected by filtration, washed with small portions of THF and 2-propanol, sequentially, and then dried. Purification of this dry raw product was performed by suspending it in approx. 400 ml of 2-propanol, breaking down particles to a uniform size with a low power ultrasonic bath and decanting the homogeneous suspension from remaining larger particles. This suspension was then filtrated again (requires frit with small pore size, min. Por. 3), washed with 2-propanol and the obtained residue dried thoroughly to yield 574.90 mg of a white solid (0.46 mmol, 28.9 %). This is in principle the procedure used by Gelinsky et al.[33] to obtain substituted BTAs.



^{1}H NMR (700 MHz, TFA-d$_0$, 300K, ref.: TFA = 11.50 ppm): δ = 8.72 (s, 3H^1), 8.33 (m, 3H^4), 7.96 (br s [expected: t], 3H^7), 4.44 (m, 3H^5), 3.42 (m, 6H^{10}), 2.32 (m, 3H^8), 1.59 (m, 6H^{11}), 1.31 (m, 6H^{12}), 1.29 (m, 6H^{13}), 1.24 - 1.12 (br m, 78H$^{14-26}$), 1.08 (d, 6.6 Hz, 9H^{9a}), 1.05 (d, 6.6 Hz, 9H^{9b}), 0.77 (t, 9H^{27}) ppm.

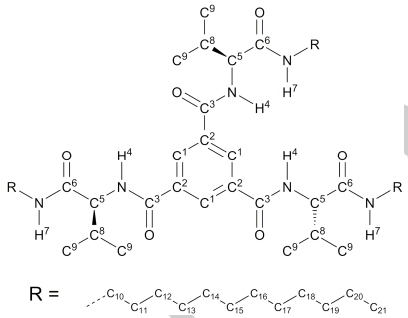
^{13}C NMR (175 MHz, TFA-d$_0$, 300K, obtained from HSQC and HMBC): δ = 174.7 (C^6), 169.6 (C^3), 133.29 (C^2), 131.63 (C^1), 62.3 (C^5), 42.0 (C^{10}), 31.90 (C$^{part\ of\ 14-26}$), 30.52 (C^8), 29.40 (C$^{part\ of\ 14-26}$), 28.92 (C^{13}), 28.23 (C^{11}), 26.52 (C^{12}), 23.32 (C$^{part\ of\ 14-26}$), 17.99 (C^{9a}), 17.86 (C^{9b}), 12.70 (C^{27}) ppm.

MS (MALDI): **expected:** 1261 u/z;
found: 1284 u/z (M+Na), 1300 u/z (M+K).
see SI section 1.2 for isotope pattern.

IR (pure solid, characteristic bands): ν_{N-H} = 3283.44 (valence), ν_{-CH2} = 2916.87 (valence), ν_{-CH2} = 2849.18 (valence), $\nu_{C=O}$ = 1637.43 (valence, amide), ν_{N-H} = 1531.64 (deformation), ν_{-CH2} = 1464.55 (deformation) cm^{-1}.

Synthesis of
N^1,N^3,N^5-tris-[L-Val-*n*-dodecyl]-benzene-1,3,5-tricarboxamide (BTA-Val-C$_{12}$)

This compound was synthesised analogous to BTA-Val-C$_{18}$ (**2**), except that after completion of the reactions, the solvent was removed in vacuo and the resulting residue purified by recrystallization from a minimal amount of 2-propanol.



^{1}H NMR (700 MHz, TFA-d$_0$, 300 K, TFA = 11.50 ppm): δ= 8.72 (s, 3H^1), 8.33 (m, 3H^4), 8.00 (s, 3H^7), 4.44 (m, 3H^5), 3.42 (m, 6H^{10}), 2.32 (m, 3H^8), 1.60 (m, 6H^{11}), 1.31 (m, 6H^{12}), 1.27 (m, 6H^{13}), 1.26 – 1.12 (br m, 42H$^{14-20}$), 1.09 (d, 6.27 Hz, 9H^{9a}), 1.06 (d, 6.27 Hz, 9H^{9b}), 0.77 (m, 9H^{21}).

^{13}C NMR (176 MHz, TFA-d$_0$, 300 K): δ= 174.5 (C^6), 169.3 (C^3), 133.1 (C^2), 131.3 (C^1), 62.1(C^5), 41.7 (C^{10}), 31.5 (C$^{part\ of\ 14-20}$), 30.2 (C^8), [29.10, 29.09, 28.99, 28.88, 28.86] (C$^{part\ of\ 14-20}$), 28.54 (C^{13}), 27.9 (C^{11}), 26.2 (C^{12}), 22.0 (C^{18}), 17.63 (C^{9a}), 17.49 (C^{9b}), 12.36 (C^{21}).

MS (MALDI): **expected:** 1008.8 u/z;
found: 1031.8 u/z (M+Na).
see SI section 1.3 for isotope pattern.

IR (pure solid, characteristic bands): ν_{N-H} = 3281.28 (valence), ν_{-CH2} = 2920.76 (valence), ν_{-CH2} = 2851.77 (valence), $\nu_{C=O}$ = 1634.53 (valence, amide), ν_{N-H} = 1532.11 (deformation), ν_{-CH2} = 1466.31 (deformation) cm^{-1}.

Acknowledgements

The authors would like to thank the Deutsche Forschungsgemeinschaft (DFG) for funding (grant TH 1115/11-1) and Volker Schmidts for assistance and helpful discussion regarding the calculation of tensors using the software RDC@hotFCHT. We thank Leon Bleichrodt for help with the synthesis of Val-BTA-C$_{12}$.

Keywords: Benzene-tricarboxamides • Alignment Media • Residual Dipolar Couplings • NMR-Spectroscopy • Self Assembly

[1] For a selection of reviews on alignment media, RDCs in general and RDC-based structure determination see: a) A. Bax, G. Kontaxis, N. Tjandra, in *Methods Enzymol., Vol. 339* (Eds.: T. L. James, V. Dötsch, U. Schmitz), Academic Press, **2001**, pp. 127-174; b) J. H. Prestegard, C. M. Bougault, A. I. Kishore, *Chem. Rev.* **2004**, *104*, 3519-3540; c) C. M. Thiele, *Concepts Magn. Reson., Part A* **2007**, *30A*, 65-80; d) C. M. Thiele, *Eur. J. Org. Chem.* **2008**, *2008*, 5673-5685; e) G. Kummerlöwe, B. Luy, *TrAC, Trends Anal. Chem.* **2009**, *28*, 483-493; f) R. R. Gil, *Angew. Chem. Int. Ed.* **2011**, *50*, 7222-7224; g) R. R. Gil, *Angew. Chem.* **2011**, *123*, 7360-7362; h) V. Schmidts, *Magn. Reson. Chem.* **2017**, *55*, 54-60.

[2] D. Neuhaus, M. P. Williamson, *The Nuclear Overhauser Effect in Structural and Conformational Analysis*, 2 ed., John Wiley & Sons Ltd, Chichester, West Sussex, England, **2000**.

[3] a) M. Karplus, *J. Chem. Phys.* **1959**, *30*, 11-15; b) M. Karplus, *J. Am. Chem. Soc.* **1963**, *85*, 2870-2871; c) C. A. G. Haasnoot, F. A. A. M. de Leeuw, C. Altona, *Tetrahedron* **1980**, *36*, 2783-2792.

[4] For the understanding of the theoretical background the following article is recommended: F. Kramer, M. V. Deshmukh, H. Kessler, S. J. Glaser, *Concepts Magn. Reson., Part A* **2004**, *21A*, 10-21.

[5] a) A. Saupe, G. Englert, *Phys. Rev. Lett.* **1963**, *11*, 462-464; b) A. Saupe, *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 97-112.

[6] a) J. R. Tolman, J. M. Flanagan, M. A. Kennedy, J. H. Prestegard, *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 9279-9283; b) N. Tjandra, A. Bax, *Science* **1997**, *278*, 1111-1114.

[7] a) E. Troche-Pesqueira, M.-M. Cid, A. Navarro-Vazquez, *Org. Biomol. Chem.* **2014**, *12*, 1957-1965; b) M. E. Di Pietro, G. Celebre, G. De Luca, *J. Magn. Reson.* **2016**, *267*, 63-67.

[8] C. M. Thiele, W. C. Pomerantz, N. L. Abbott, S. H. Gellman, *Chem. Commun.* **2011**, *47*, 502-504.

[9] a) X. Lei, F. Qiu, H. Sun, L. Bai, W.-X. Wang, W. Xiang, H. Xiao, *Angew. Chem. Int. Ed.* **2017**, *56*, 12857-12861; b) X. Lei, F. Qiu, H. Sun, L. Bai, W.-X. Wang, W. Xiang, H. Xiao, *Angew. Chem.* **2017**, *129*, 13037-13041.

[10] a) K. Czarniecka, E. T. Samulski, *Mol. Cryst. Liq. Cryst.* **1981**, *63*, 205-214; b) A. Meddour, I. Canet, A. Loewenstein, J. M. Pechine, J. Courtieu, *J. Am. Chem. Soc.* **1994**, *116*, 9652-9656; c) M. Sarfati, J. Courtieu, P. Lesot, *Chem. Commun.* **2000**, 1113-1114; d) C. Aroulanda, M. Sarfati, J. Courtieu, P. Lesot, *Enantiomer* **2001**, *6*, 281-287; e) A. Marx, C. Thiele, *Chem. Eur. J.* **2009**, *15*, 254-260; f) L. Arnold, A. Marx, C. M. Thiele, M. Reggelin, *Chem. Eur. J.* **2010**, *16*, 10342-10346; g) M. Dama, S. Berger, *Org. Lett.* **2012**, *14*, 241-243; h) N.-C. Meyer, A. Krupp, V. Schmidts, C.

M. Thiele, M. Reggelin, *Angew. Chem. Int. Ed.* **2012**, *51*, 8334-8338; i) N.-C. Meyer, A. Krupp, V. Schmidts, C. M. Thiele, M. Reggelin, *Angew. Chem.* **2012**, *124*, 8459-8463; j) P. Lesot, C. Aroulanda, H. Zimmermann, Z. Luz, *Chem. Soc. Rev.* **2015**, *44*, 2330-2375; k) S. Hansmann, V. Schmidts, C. Thiele, *Chem. Eur. J.* **2017**, *23*, 9114-9121; l) M. Schwab, D. Herold, C. M. Thiele, *Chem. Eur. J.* **2017**, *23*, 14576-14584.

[11] a) B. Deloche, E. T. Samulski, *Macromolecules* **1981**, *14*, 575-581; b) Y. Ishii, M. A. Markus, R. Tycko, *J. Biomol. NMR* **2001**, *21*, 141-151; c) B. Luy, K. Kobzar, H. Kessler, *Angew. Chem. Int. Ed.* **2004**, *43*, 1092-1094; d) B. Luy, K. Kobzar, H. Kessler, *Angew. Chem.* **2004**, *116*, 1112-1115; e) J. C. Freudenberger, P. Spiteller, R. Bauer, H. Kessler, B. Luy, *J. Am. Chem. Soc.* **2004**, *126*, 14690-14691; f) R. R. Gil, C. Gayathri, N. V. Tsarevsky, K. Matyjaszewski, *J. Org. Chem.* **2008**, *73*, 840-848; g) G. Kummerlöwe, M. U. Kiran, B. Luy, *Chem. Eur. J.* **2009**, *15*, 12192-12195; h) C. Gayathri, N. V. Tsarevsky, R. R. Gil, *Chem. Eur. J.* **2010**, *16*, 3622-3626; i) C. Merle, G. Kummerlöwe, J. C. Freudenberger, F. Halbach, W. Stöwer, C. L. v. Gostomski, J. Höpfner, T. Beskers, M. Wilhelm, B. Luy, *Angew. Chem. Int. Ed.* **2013**, *52*, 10309-10312; j) C. Merle, G. Kummerlöwe, J. C. Freudenberger, F. Halbach, W. Stöwer, C. L. v. Gostomski, J. Höpfner, T. Beskers, M. Wilhelm, B. Luy, *Angew. Chem.* **2013**, *125*, 10499-10502; k) M. E. García, S. R. Woodruff, E. Hellemann, N. V. Tsarevsky, R. R. Gil, *Magn. Reson. Chem.* **2016**, *55*, 206-209; l) Y. E. Moskalenko, V. Bagutski, C. M. Thiele, *Chem. Commun.* **2017**, *53*, 95-98.

[12] A. R. Hirst, I. A. Coates, T. R. Boucheteau, J. F. Miravet, B. Escuder, V. Castelletto, I. W. Hamley, D. K. Smith, *J. Am. Chem. Soc.* **2008**, *130*, 9113-9121.

[13] a) G. Kummerlöwe, E. F. McCord, S. F. Cheatham, S. Niss, R. W. Schnell, B. Luy, *Chem. Eur. J.* **2010**, *16*, 7087-7089; b) T. Montag, C. M. Thiele, *Chem. Eur. J.* **2013**, *19*, 2271-2274.

[14] P. W. Kuchel, B. E. Chapman, N. Müller, W. A. Bubb, D. J. Philp, A. M. Torres, *J. Magn. Reson.* **2006**, *180*, 256-265.

[15] a) A. Krupp, Ph. D. thesis, TU Darmstadt (Darmstadt), **2015**; b) A. Kreiter, Ph. D. thesis, TU Darmstadt (Darmstadt), **2017**; c) S. Jeziorowski, C. M. Thiele, *Chem. Eur. J.* **2018**, *24*, 15631-15637.

[16] a) M. Leyendecker, N.-C. Meyer, C. M. Thiele, *Angew. Chem. Int. Ed.* **2017**, *56*, 11471-11474; b) M. Leyendecker, N.-C. Meyer, C. M. Thiele, *Angew. Chem.* **2017**, *129*, 11629-11632.

[17] a) L. Brunsveld, A. P. H. J. Schenning, M. A. C. Broeren, H. M. Janssen, J. A. J. M. Vekemans, E. W. Meijer, *Chem. Lett.* **2000**, *29*, 292-293; b) M. M. J. Smulders, T. Buffeteau, D. Cavagnat, M. Wolffs, A. P. H. J. Schenning, E. W. Meijer, *Chirality* **2008**, *20*, 1016-1022; c) S. Cantekin, T. F. A. de Greef, A. R. A. Palmans, *Chem. Soc. Rev.* **2012**, *41*, 6125-6137.

[18] A. J. Markvoort, H. M. M. ten Eikelder, P. A. J. Hilbers, T. F. A. de Greef, E. W. Meijer, *Nat. Commun.* **2011**, *2*, 509.

[19] P. J. M. Stals, M. M. J. Smulders, R. Martín-Rapún, A. R. A. Palmans, E. W. Meijer, *Chem. Eur. J.* **2009**, *15*, 2071-2080.

[20] a) M. M. Green, M. P. Reidy, R. D. Johnson, G. Darling, D. J. O'Leary, G. Willson, *J. Am. Chem. Soc.* **1989**, *111*, 6452-6454; b) M. M. J. Smulders, A. P. H. J. Schenning, E. W. Meijer, *J. Am. Chem. Soc.* **2008**, *130*, 606-611.

[21] C. M. A. Leenders, T. Mes, M. B. Baker, M. M. E. Koenigs, P. Besenius, A. R. A. Palmans, E. W. Meijer, *Mater. Horiz.* **2014**, *1*, 116-120.

[22] a) J. J. van Gorp, J. A. J. M. Vekemans, E. W. Meijer, *J. Am. Chem. Soc.* **2002**, *124*, 14759-14769; b) Y. Ishioka, N. Minakuchi, M. Mizuhata, T. Maruyama, *Soft Matter* **2014**, *10*, 965-971.

[23] T. Shikata, D. Ogata, K. Hanabusa, *J. Phys. Chem. B* **2004**, *108*, 508-514.

[24] a) Y. Dai, X. Zhao, X. Su, G. Li, A. Zhang, *Macromol. Rapid Commun.* **2014**, *35*, 1326-1331; b) P. Ahlers, H. Frisch, P. Besenius, *Polym. Chem.* **2015**, *6*, 7245-7250; c) A. Desmarchelier, M. Raynal, P. Brocorens, N. Vanthuyne, L. Bouteiller, *Chem. Commun.* **2015**, *51*, 7397-7400; d) A. Desmarchelier, B. G. Alvarenga, X. Caumes, L. Dubreucq, C. Troufflard, M. Tessier, N. Vanthuyne, J. Ide, T. Maistriaux, D. Beljonne, P. Brocorens, R. Lazzaroni, M. Raynal, L. Bouteiller, *Soft Matter* **2016**, *12*, 7824-7838; e) K. K. Bejagam, R. C. Remsing, M. L. Klein, S. Balasubramanian, *Phys. Chem. Chem. Phys.* **2017**, *19*, 258-266; f) M. de Loos, J. H. van Esch, R. M. Kellogg, B. L. Feringa, *Tetrahedron* **2007**, *63*, 7285-7301.

[25] A. El-Faham, F. Albericio, *Chem. Rev.* **2011**, *111*, 6557-6602.

[26] a) P. Besenius, K. P. van den Hout, H. M. H. G. Albers, T. F. A. de Greef, L. L. C. Olijve, T. M. Hermans, B. F. M. de Waal, P. H. H. Bomans, N. A. J. M. Sommerdijk, G. Portale, A. R. A. Palmans, M. H. P. van Genderen, J. A. J. M. Vekemans, E. W. Meijer, *Chem. Eur. J.* **2011**, *17*, 5193-5203; b) A. Karmakar, C. L. Oliver, A. E. Platero-Prats, E. Laurila, L. Ohrstrom, *CrystEngComm* **2014**, *16*, 8243-8251.

[27] A. Sakamoto, D. Ogata, T. Shikata, O. Urakawa, K. Hanabusa, *Polymer* **2006**, *47*, 956-960.

[28] I. O. Shklyarevskiy, P. Jonkheijm, P. C. M. Christianen, A. P. H. J. Schenning, A. Del Guerzo, J.-P. Desvergne, E. W. Meijer, J. C. Maan, *Langmuir* **2005**, *21*, 2108-2112.

[29] a) R. Berger, C. Fischer, M. Klessinger, *J. Phys. Chem. A* **1998**, *102*, 7157-7167; b) C. M. Thiele, V. Schmidts, B. Böttcher, I. Louzao, R. Berger, A. Maliniak, B. Stevensson, *Angew. Chem. Int. Ed.* **2009**, *48*, 6708-6712; c) C. M. Thiele, V. Schmidts, B. Böttcher, I. Louzao, R. Berger, A. Maliniak, B. Stevensson, *Angew. Chem.* **2009**, *121*, 6836-6840; d) V. Schmidts, Ph. D. thesis, TU Darmstadt (Darmstadt), **2013**.

[30] G. Cornilescu, J. L. Marquardt, M. Ottiger, A. Bax, *J. Am. Chem. Soc.* **1998**, *120*, 6836-6837.

[31] A. Enthart, J. C. Freudenberger, J. Furrer, H. Kessler, B. Luy, *J. Magn. Reson.* **2008**, *192*, 314-322.

[32] a) K. Fehér, S. Berger, K. E. Kövér, *J. Magn. Reson.* **2003**, *163*, 340-346; b) C. M. Thiele, W. Bermel, *J. Magn. Reson.* **2012**, *216*, 134-143.

[33] M. Gelinsky, R. Vogler, H. Vahrenkamp, *Inorg. Chem.* **2002**, *41*, 2560-2564.

[34] V. Theodorou, K. Skobridis, A. G. Tzakos, V. Ragoussis, *Tetrahedron Lett.* **2007**, *48*, 8230-8233.

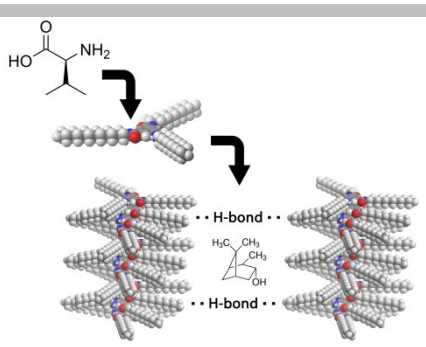
10.1002/ejoc.201801306

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

FULL PAPER

We present a modified version of our original BTA-monomers, containing an additional L-valine moiety. Through this modification, the number of available hydrogen bond acceptors/donators per monomer is doubled, resulting in vastly increased stability. The new system thus obtained exhibits anisotropic properties at much lower concentrations of BTA and allows for the determination of residual dipolar couplings for previously incompatible analytes.



Alignment Media, Supramolecular Polymers

*Kevin Knoll, Martin Leyendecker, and Christina M. Thiele**

Page No. – Page No.

L-Valine derivatised 1,3,5-Benzene-tricarboxamides as Building Blocks for a new Supramolecular Organogel-like Alignment Medium