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Synthesis of per-deuterated alkyl amines for the preparation of deuterated organic pyromellitamide gelators

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ABSTRACT

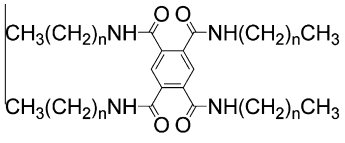
A general, direct and scalable synthesis of per-deuterated alkyl amines is reported, together with their incorporation into pyromellitamides, which form self-assembled gels in cyclohexane. The deuterium labelling of these gelators allows the study of the dynamic intermolecular interactions in these materials using solid-state ^{2}H NMR spectroscopy.

Research into self-assembled gels is a rapidly expanding field due to their numerous technological,[1] biomaterial and medical applications,[2] ranging from targeted drug delivery[3] to artificial muscle fibres,[4] and even formation of scaffolds for the regeneration of spinal cords.[5] The design and synthesis of organic molecule based self-assembling gels has advanced rapidly over the last two decades.[6] Although gelator molecules are readily designed and assembled, detailed structural analysis of these molecules in the gel phase remains a significant challenge.

We have demonstrated that a new family of gelator molecules, the pyromellitamides **1** and **2** in Figure 1, form organogels in non-polar solvents such as cyclohexane at ~1% w/w.[7] Intermolecular hydrogen-bonds and π–π interactions allow these molecules to assemble into one-dimensional fibres of ~2 nm in diameter. Pyromellitamides then aggregate into higher-order hierarchical assemblies and show evidence of forming bundles of twisted helical fibres (of hundreds of nm) and ultimately a three-dimensional network resulting in gel formation.[7b] Techniques such as electron microscopy and atomic force microscopy, while useful for imaging these gel structures in the dry state, do not allow the structure of these pyromellitamide organogels to be quantified in their fully solvated state. In situ studies of solvated gel structures require techniques such as NMR and small angle neutron scattering (SANS) in conjunction with deuterium labelling in order to differentiate between the gel fibre network and surrounding solvent matrix. Furthermore, ^{2}H NMR line shapes are sensitive to the rate and mechanism of the particular re-orientational motion of the C–D bond. Line shape analysis using appropriate simulation programs can give important information on the motional behaviour of molecules in gel matrices.

Simple amide- and urea-based gelators derived from alkyl amines feature heavily in the literature on self-assembled gels.[1,6] Methods to more effectively per-deuterate amines are therefore of general interest to this research area. We report here the synthesis of per-deuterated alkyl amines which can then be integrated into the pyromellitamides. We demonstrate the utility of deuteration by solid-state ^{2}H NMR analysis of the resulting compounds giving us valuable insight into the mobility of the alkyl side chains.

Deuterium-labelled compounds are commonly used for determination of structure,[8] reaction pathways,[9] as stable isotope tracers,[10] for the synthesis of drug compounds with improved



n = 3: **1**
n = 5: **2**

Figure 1. Pyromellitamide gelator.

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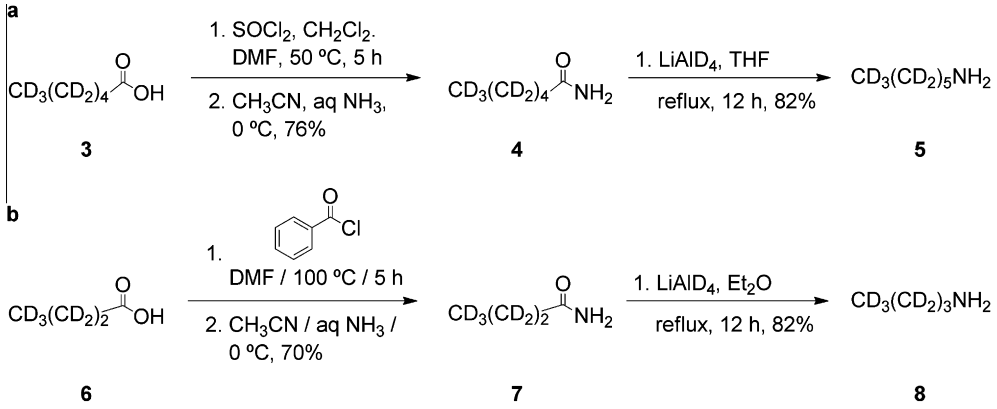

Scheme 1. Synthesis of deuterated amines **5** and **8** from the corresponding perdeuterated fatty acids **3** and **6**.

metabolic stability,[11] and to provide enhanced contrast in neutron scattering studies.[12] Deuterium labelled aliphatic alkyl amines cannot be produced directly by hydrothermal exchange methods using metal catalysts at high temperature and pressure,[13a–c] as they lead to oxidation of the amine groups.

Mixed results have been obtained by those attempting to deuterate aliphatic amines under more moderate conditions. Only a few examples of the H/D-exchange of amines using heterogeneous catalysts are known.[13d] In most of these cases, H/D exchange reactions suffer from only moderate deuterium incorporation. Depending on the position of the amine along the aliphatic chain (i.e., 1°, 2° or 3° amine), exchange may occur at alpha, beta and/or in rare cases, at the gamma positions.[13] Desai et al.[14] used the basic nature of the alkyl amine to help deuterate these molecules at ~120 °C using platinum chloride reduced by $NaBH_4$; however only the α- and β-positions showed significant levels of deuteration.[14] For *n*-butylamine-d_4 the deuteration levels of the α- and β-positions were 82% and 21%; while for *n*-hexylamine-d_4 deuteration levels were found to be 62% and 36%, respectively.

Homogeneous transition metal catalysts are more commonly used to allow for selective H/D exchange of amines.[15] Takahashi et al.[15a] and Alexakis et al.[15b] have used Ru-based catalysts to deuterate selectively the α-positions of 1° and 2° amines, and the α- and β-positions of 2° amines, respectively. Beller and co-workers[15c] also demonstrated chemoselective deuteration of the α- and β-positions of tertiary amines using a ruthenium Shvo catalyst.

Deuterating the hydrocarbon chain of aliphatic amines beyond their α-, β- and γ-positions becomes impossible using the above methods with moderate conditions. This is due to the inactive nature of the carbon sites that are situated away from the amine group. Moreover, the harsher conditions of the hydrothermal exchange reactions can lead to oxidation of the amine groups. Therefore, in order to achieve the complete deuteration of the hydrocarbon chains of these aliphatic amines, it is necessary to firstly produce per-deuterated forms of stable precursors (i.e., fatty acids) before converting them into their respective amine. This Letter reports optimized methods for the production of per-deuterated **5** and **8**, and the details of their assembly into the deuterated pyromellitamide gelators **10** and **11**, to demonstrate their capacity as effective probes in ^2H NMR measurements.

The per-deuterated amines **5** and **8** were synthesized using per-deuterated *n*-hexanoic acid-d_{11} **3** and *n*-butanoic acid-d_7 **6**, respectively, as starting materials (Scheme 1). Starting from *n*-hexanoic acid, **3** was prepared using 10% Pt/C (4% w/w) and D_2O under basic conditions in a Parr reactor at 220 °C for two cycles, each of 3 days. This hydrothermal process gave **3** with 97(±2)% deuterium exchange and over 75% yield (Supplementary data, Figs. S1 and S2). The same protocol was used to produce **6** from *n*-butanoic acid in 70% yield [98(±2)% deuteration—Supplementary data, Figs. S3 and S4]. The overall level of deuteration within each of these molecules was determined using ESI-mass spectrometry for both **3** and **6**.

The method for converting the carboxylic acid (i.e., C_4 and C_6) into the corresponding amine needs to consider critically the high volatility of the possible common intermediate compounds that are usually produced in such reactions (e.g., alcohol, bromides, or azides). To obtain the targeted per-deuterated amine **5** (Scheme 1a), **3** was treated with excess thionyl chloride in dichloromethane at 0 °C. After adding a catalytic amount of *N*,*N*-dimethylformamide, the reaction was stirred for 5 h at reflux temperature. Excess thionyl chloride was then distilled off and the residue taken into dry acetonitrile and cooled to 0 °C. Aqueous ammonia was added slowly and the mixture stirred for 2 h at room temperature.[16] The mixture was partitioned into dichloromethane and upon evaporation the residue was purified by flash column chromatography to give a white solid, *n*-hexamide-d_{11} **4** in 76% yield. Amide **4** was then successfully reduced to give **5** using $LiAlD_4$ in tetrahydrofuran at 70 °C. The amine was then purified by distillation through a Vigreux column at 100 mbar pressure and 70 °C, giving **5** in 82% yield. Deuteration levels were found to be retained at 98% (Supplementary data, Figs. S5–S7).

For the equivalent reaction scheme, the synthesis of per-deuterated **8** from **6** would be complicated by the fact that the boiling point of the intermediate butyryl chloride is similar to that of thionyl chloride, making the removal of the latter from the reaction mixture difficult, prior to the conversion into the amide. We therefore chose a different approach for this step of the synthesis (Scheme 1b); using benzoyl chloride as the chlorinating agent instead of thionyl chloride.[17] The optimized reaction conditions used 3 mol equiv of benzoyl chloride and 1 mol equiv of **6**, heating under refluxing conditions for 30 min, before distilling off the desired butyryl chloride intermediate. Conversion of this acid chloride into the *n*-butylamide-d_7 **7** (solid, 70% yield) was achieved under the same conditions described above.

Due to the similarity in boiling points between **8** and tetrahydrofuran, the reduction of **7** was carried out in diethyl ether at reflux temperature overnight before distillation through a Vigreux column at ambient pressure. The required product **8** was obtained in good yield (82%). It should be noted that the reduction of **7** was also attempted in diglyme and tetraglyme as high boiling ether solvents, however the amide was not sufficiently soluble in these solvents. The deuteration levels of **8** were found to be retained at 97% (Supplementary data, Figs. S8–S10).

The deuterated pyromellitamide gelators **11** and **10** were prepared according to the method of Tong et al.[7b] In brief, a solution of benzene-1,2,4,5-tetracarbonyl tetrachloride (**9**)[18] in dry THF