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Synthesis of enantiomerically pure functionalised trianglamine macrocycles by N-acylation and N-alkylation reactions

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Abstract—The N-alkylation and N-acylation reactions of trianglamine macrocycles are described leading to an efficient synthesis of enantiomerically pure functionalised hexa-amide and hexa-amine trianglamine macrocycles.

In recent years supramolecular chemistry has emerged as one of the most actively pursued fields of the chemical sciences. Its implications now reach from the basis of molecular recognition in natural systems such as protein substrate interactions to exciting new applications in chemical technology and material sciences.[1,2] Among the most promising applications of molecular recognition is certainly chiral recognition necessitating the development of efficient synthetic methodology for the synthesis of novel enantiomerically pure macrocyclic receptors.

Following initial work by Gawronski et al.,[3] we and others, have recently reported on a class of enantiomerically pure hexa-imine macrocycles, obtained from a [3+3] cyclocondensation strategy, which we have named trianglimines and trianglamines in which the imines have been reduced to give hexa-amine macrocycles.[4–9]

Within this publication we comment on the scope and limitations of N-acylation reactions of trianglamines leading to hexa-amide macrocycles and N-alkylation reactions leading to functionalised hexa amine derivatives. This contribution therefore clearly illustrates the versatility of trianglamine macrocycles for the development of highly functionalised chiral synthetic receptors.

In an optimised procedure, trianglamine **1** is available after reduction of the parent trianglimine in a two-step reaction sequence on a multi-gram scale in almost quantitative yield. With large quantities of material in hand we investigated the functionalisation reactions initially focussing on the reactivity of the six nucleophilic amine nitrogens.

Acylation with acetyl chloride in acetonitrile gave the hexa-amide macrocycle **2a** in almost quantitative yield.[10] The ESI mass spectrum showed a single molecular ion at m/z 923.9 as expected for M+Na ($C_{54}H_{73}NaN_6O_6$) (Fig. 1). The ^{1}H NMR spectrum showed one set of signals for the three repeating units. The HCNC=O protons of the 1,2 diamine core is characteristically

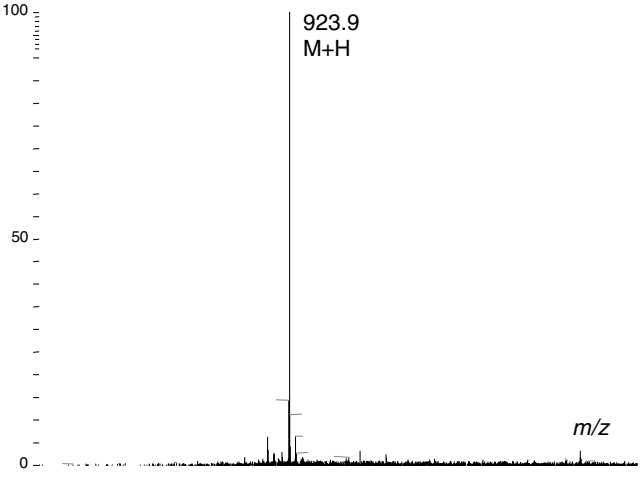

Figure 1. ESI mass spectrum of hexa-amide macrocycle **2a** (M+Na for $C_{54}H_{73}NaN_6O_6$).

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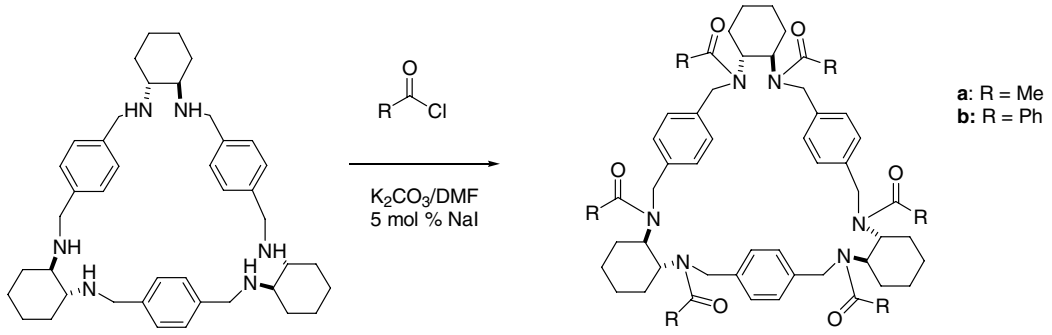
shifted downfield as well as the two diastereotopic CH_2N protons as compared with the hexa-amine **1**. Acylation with benzoyl chloride gave, after 12 h of reaction time, a statistical mixture of the tetra-benzoyl compound and the hexa-benzoyl derivative **2b** as judged by the ESI mass spectrum of the crude reaction mixture. Surprisingly, no other amide could be detected. Prolonged reaction time led to the exclusive formation of the hexa-amide **2b**, which again could be isolated in almost quantitative yield. The signals in the ^1H NMR spectrum of **2b** were broad as expected for a molecule of this nature.



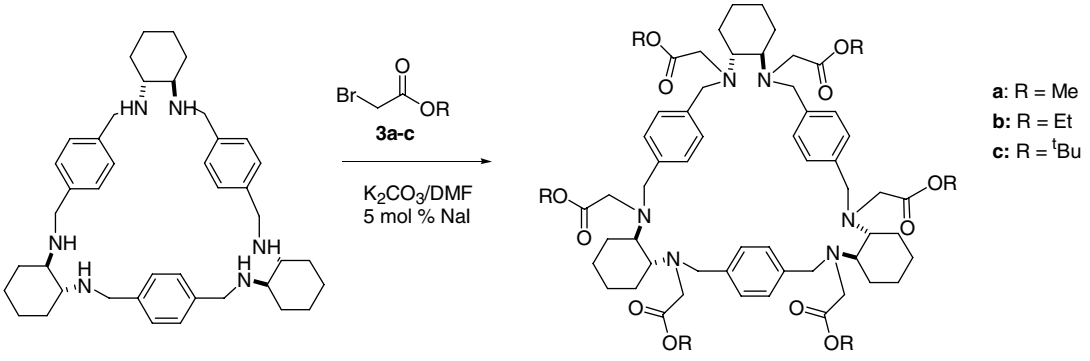
(*2R, 3R, 12R, 13R, 22R, 23R*)-**1**

(*2R, 3R, 12R, 13R, 22R, 23R*)-**2a,b**

Next, we turned our attention to the N-alkylation of the six trianglamine nitrogens. Alkylation with a series of different bromoacetate esters **3a**–**c** in DMF using K_2CO_3 as base gave the tertiary amines **4a**–**c** in excellent yields. The compounds always crystallised as their DMF adducts and yields are given in Table 1. The ESI mass spectra of all the compounds showed a single molecular ion at the expected *m*/*z* value and the ^1H NMR spectra showed one set of signals for the three repeating units.[11] The CH_2 protons are diastereotopic due to the six stereogenic centres in the cyclohexane rings. All the signals were unambigiously assigned using ^1H–^1H-COSY and ^1H–^{13}C-HSQC techniques. Attempts to obtain selectively mono and di-alkylated trianglamines failed and in all cases statistical mixture of products were obtained as was evident from the ESI mass spectra of the crude products.

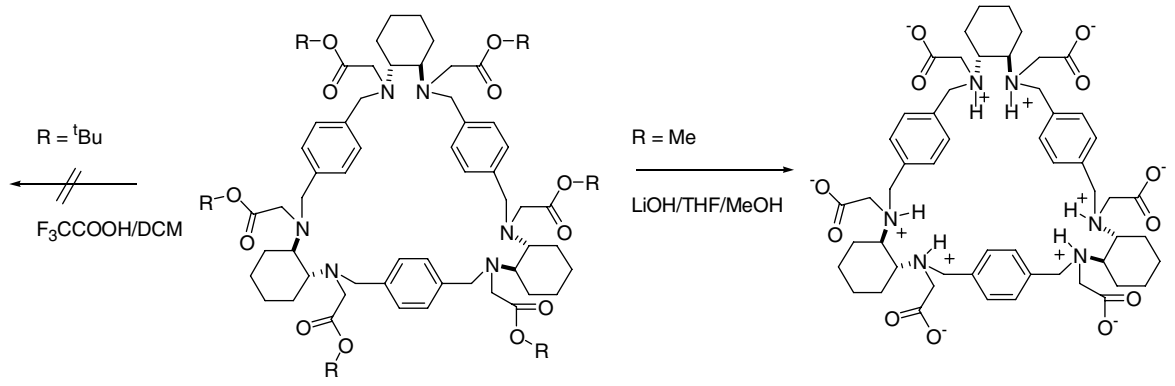
With the acetate esters in hand we decided to investigate deprotection of the ester functionality to give hexa-carboxylic acid derivatives, which potentially seem attractive receptors for molecular recognition in aqueous solutions. Surprisingly all attempts to deprotect the *tert*-butyl derivative **4c** using standard conditions with trifluoroacetic acid in dichloromethane failed. In all cases a syrup-like material displaying extremely broad bands in the ^1H NMR spectrum was obtained. The ESI mass spectra of the crude reaction showed only products of partial deprotection. Hence, we attempted base-induced deprotection. Reaction of the methyl acetate **4a** with LiOH in THF/methanol afforded the desired hexa-carboxylic acid **5** in excellent yield. According to the ^1H NMR spectrum compound **5** exists, interestingly, as the hexa-zwitterion shown in $CDCl_3$ solution. This follows directly from the chemical shift of the ammonium ion proton at 5.34 ppm, which according to the ^1H–^1H-COSY spectrum couples to both of the two diastereotopic sets of methylene protons. It is worth noting that this compound can formally be regarded as a hexa-amino acid.

Finally, we turned our attention to the reaction of trianglamine **1** with difunctionalised electrophiles such as alkyl dihalides. Our initial aim here was to exploit the unique topology of the macrocycle displaying three basic nitrogens above and three basic nitrogens below the plane formed by any three aromatic quaternary car-



(*2R, 3R, 12R, 13R, 22R, 23R*)-**1**

(*2R, 3R, 12R, 13R, 22R, 23R*)-**4a-c**



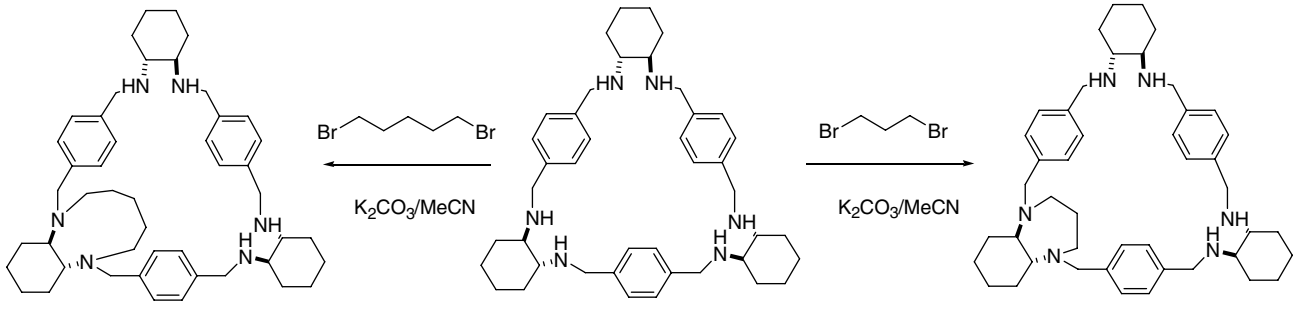
(2R, 3R, 12R, 13R, 22R, 23R)-**4a,c**

(2R, 3R, 12R, 13R, 22R, 23R)-**5**

Table 1. Yields and selected spectroscopic data for macrocycles **2a**,**b**, **4a**–**c** and **5**–**7**

Compound	Yield (%)	MS *m*/*z*	Compound	Yield (%)	MS *m*/*z*
2a	97	923.9	**4c**	91	1333.9
2b	95	1273.2	**5**	97	997.5
4a	89	1081.6	**6**	24	689.5
4b	79	1165.5	**7**	22	717.6

bons to obtain tube like structures by polymerisation reactions. Reaction of **1** with an excess of 1,3-dibromopropane in acetonitrile gave, according to the ESI mass spectrum of the crude reaction, a mixture of compounds consisting of mono-alkylated and dialkylated species along with two species with a propane moiety bridging two nitrogens. No traces of a dimeric or oligomeric product, in which two macrocycles were linked via a propane bridge, could be detected. It appeared as if intramolecular N-alkylation dominated over intermolecular dialkylation. In order to learn about the influence of the chain length of the dibromide, we carried out the same reaction using 1,4-dibromobutane, 1,5-dibromopentane, 1,6-dibromohexane and 1,8-dibromooctane. In all cases no product of intermolecular dialkylation could be detected. As the main product, compounds with alkyl bridges bridging two basic nitrogen atoms could be detected. After optimisation of the reaction conditions the main product from the reaction with 1,3-dibromopropane and 1,5-dibromopentane could be isolated in pure form using preparative thin layer chromatography. The isomeric purity of the compounds **6** and **7** was analysed by ESI mass spectrometry, NMR spectroscopy and HPLC. Detailed 2-D NMR investigations including ^{1}H–^{1}H-COSY, ^{1}H–^{13}C-HSQC and ^{1}H–^{13}C-HMBC revealed the product to be the C_2 symmetric 1,4-bridged macrobicycles **6** and **7**. The NMR spectra revealed a C_2-symmetric compound whose overall H–C connectivities were in perfect agreement with the structure. Molecular modelling also indicated that the 1,4-bridged species is the only reaction product free of excessive strain energy as compared to alternative regioisomeric bicyclic structures.



(2R, 3R, 12R, 13R, 22R, 23R)-**7**

(2R, 3R, 12R, 13R, 22R, 23R)-**1**

(2R, 3R, 12R, 13R, 22R, 23R)-**6**

In conclusion, we have shown that trianglamine macrocycles are suitable precursors for the synthesis of functionalised chiral macrocycles using N-acylation and N-alkylation reactions. The ease of functionalisation underlines the versatility of this class of compounds as receptors in supramolecular chemistry in particular for chiral recognition.

Acknowledgements

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10. Analytical data for **2a**: mp 225–230 °C; ^{1}H NMR δ_H (500 MHz in $CDCl_3$): 1.19–1.90 (24H, m, CH_2), 2.00 (18H, s, CH_3), 4.50 (6H, ABq, *J* 19 Hz, CH_AH_BN), 4.54 (6H, ABq, *J* 19 Hz, CH_BH_AN), 4.81 (6H, s, broad, HCNAc), 7.17 (12H, s, Ar); MS: *m*/*z* (ESI) 923.9 (M+Na); CHN found: C, 72.9; H, 8.04; N, 8.88. $C_{54}H_{72}N_6O_6$ requires: C, 72.0; H, 8.00; N, 9.30.
11. Analytical data for **4a**: mp 187–189 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H: 8.93 (s, 2H, DMF), 7.25 (12H, s, ArH), 3.88 (6H, d, *J* 13.1 Hz, CH_AH_BAr), 3.60 (18H, s, OMe), 3.53 (6H, d, *J* 13.1 Hz, CH_AH_BAr), 3.45 (6H, d, *J* 17.1 Hz, CH_AH_BCO), 3.37 (6H, d, *J* 17.1 Hz, CH_AH_BCO), 2.95 (s, 6H, DMF), 2.74 (s, 6H, DMF), 2.71 (12H, m, br, CHN), 2.07 (6H, m, br CH_2), 1.72–1.66 (12H, m, br CH_2), 1.11 (6H, m, br CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C: 173.5 (C=O), 162.5 (DMF), 138.5, 129.2, 61.5, 54.0, 51.3, 36.5, 31.6 (DMF), 27.1, 26.1; 21.1; *m*/*z* (FAB) 1081 (M+H); (ESI) 1081.6 (M+H); CHN $C_{60}H_{84}N_6O_{12}$ 2DMF requires: C, 64.58, H, 8.05, N, 9.13; found: C, 64.71, H, 8.11, N, 9.14.