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Efficient N- and C-functionalisation of cyclam macrocycles utilising bisaminal methodology

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Abstract—An efficient synthesis of C-functionalised cyclam macrocycles that employs bisaminal intermediates and allows N-substitution to be controlled is reported.

There is much current interest in the applications of bifunctional chelators based on tetraazamacrocycles such as 1,4,8,11-tetraazacyclotetradecane (cyclam) to biology and medicine, for example, MRI contrast agents and radioimmunotherapy.[1,2] In particular, a great deal of research effort in this area has been focused on 6-(4-aminobenzyl)-1,4,8,11-tetraazacyclotetradecane-*N*,*N*,*N*,*N*-tetraacetic acid and its analogues.[3] Consequently, there is an increasing requirement for versatile and efficient routes to the 4-nitrobenzyl- or 4-cyanobenzyl derivatives of 6-C-functionalised 1,4,8,11-tetraazacyclotetradecane (cyclam), both of which can be reduced and further reacted to form suitable precursors for conjugation to biomolecules.[3,4] The ideal synthetic strategy will include a number of key aspects: an efficient cyclisation step involving inexpensive, readily available starting materials, the ability to produce gram quantities of C-functionalised cyclam macrocycles, and lastly, provide straightforward access to a range of selectively N-substituted systems. Towards this goal we present herein a novel and efficient route to N- and C-functionalised cyclam macrocycles in which a 4-nitrobenzyl group is appended at the 6-position.

Recently, the use of bisaminal intermediates both as organic templates for cyclisation reactions and as a protecting group for selective N-functionalisation has been highly successful.[5–10] In a novel approach to the preparation of cyclam, *N*,*N*-bis(2-aminoethyl)-1,3-propanediamine was rigidified by condensation with butanedione to form a bisaminal **1** prior to reaction with 1,3-dibromopropane.[5] Compared to other published routes the method is very attractive, requiring only mild conditions and having a relatively short reaction time (6 h at rt).[6] Regioselective N-functionalisation of cyclam macrocycles is a continuing synthetic challenge, although there are a number of different strategies proposed.[7] One common method involves addition of a large excess of macrocycle relative to the electrophile in order to limit N-derivatisation to one, two or three sites. Even if the remaining macrocycle can be recovered at the end of the reaction, this is not an efficient approach to N-derivatisation of C-functionalised cyclam, which is prepared synthetically rather than being commercially available.[8] Alternatively, protecting groups are frequently employed to block one or more nitrogen sites on the macrocycle and so allow the remaining ones to be derivatised selectively. Although traditionally, *tert*-butyloxycarbonyl (Boc) or tosyl (Ts) groups have been used to protect the nitrogen positions of the macrocycle, new methodology with bisaminal derivatives has been developed.[9,10] On reaction of a bisaminal intermediate with an electrophile, sterically controlled N-substitution occurs cleanly and in high yield.[10] In this paper we demonstrate that by utilising bisaminals both as templates in cyclisation reactions and as protecting groups for selective N-functionalisation, an efficient method of C- and N-functionalisation is achieved. To our knowledge this is the first example of bisaminal methodology being adapted to the preparation of C-functionalised macrocycles.

The synthesis initially involves the preparation of 2-(4-nitrobenzyl)-1,3-dibromopropane **2** according to three published steps from 4-nitrobenzyl bromide and diethyl malonate, in high overall yield (66%).[12] Treatment of

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2-(4-nitrobenzyl)-1,3-dibromopropane with the butanedione derived bisaminal, **1**, in dry acetonitrile, in the presence of excess potassium carbonate and heated to 60 °C for 5 d gives rise to the cyclisation product, **3**, [74% yield after column chromatography on flash silica, 10% methanol/(3% Et_3N in CH_2Cl_2), $R_f = 0.4$].[13] The reaction mixture was monitored by ^1H NMR spectroscopy and thin layer chromatography (TLC) in order to determine the optimum conditions. It was noted that cyclisation can be achieved at rt but occurs more slowly, for example, less than 20% product was obtained after stirring the reaction mixture for 3 d. Handel and co-workers have shown that **1** exists as only the *cis*-diastereoisomer in solution, and that this bridge configuration is retained upon cyclisation using 1,3-dibromopropane.[5] By using a C-functionalised dibromo-derivative in the cyclisation step there are now two possible *cis*-diastereoisomers that can be obtained, dependent on the relative position of the hydrogen and the 4-nitrobenzyl moieties at the 6-position (Scheme 2c). The ^1H and ^{13}C NMR spectra exhibit a single set of signals for the cyclisation product, indicating that only one diastereoisomer is obtained. The single-crystal X-ray structure of **3** (Scheme 2a) confirms that the 4-nitrobenzyl moiety is in the sterically more favourable position, directed away from the methyl groups, which in turn retain their *cis*-configuration.

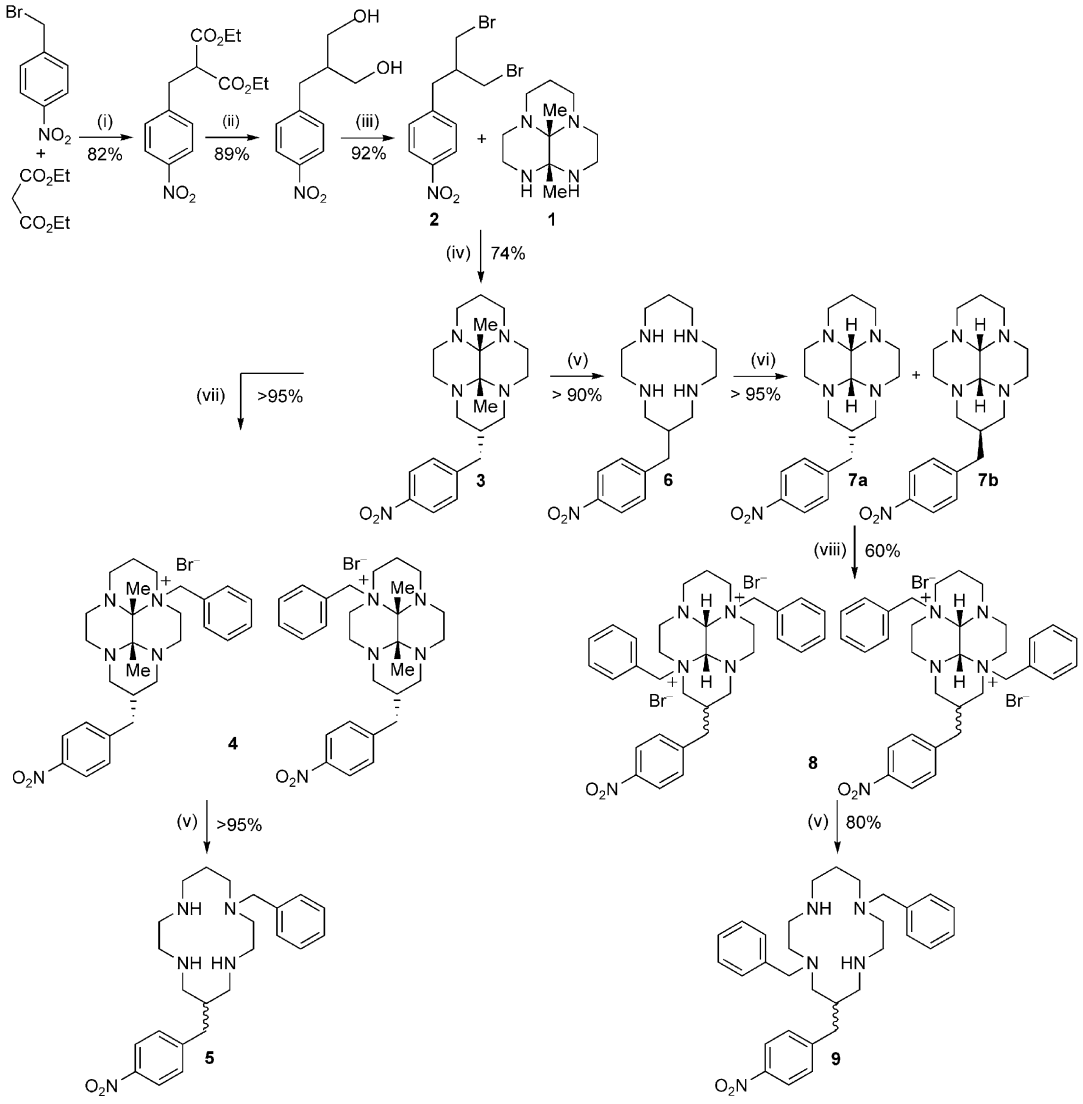
The addition of excess benzyl bromide (ca. 10 equiv) to a solution of **3** in dry acetonitrile resulted in quantitative formation of the mono-benzylated bisaminal, **4**. The ^1H and ^{13}C NMR spectra indicate that benzylation occurred selectively at one of two nitrogens on the bisaminal, and that no other diastereoisomers, or products arising from multiple substitution are obtained even after 14 d of stirring at rt. The isomer obtained is depicted in Scheme 1, in which steric repulsions between the *N*- and *C*-benzyl moieties are minimised. Other groups have observed exceptional selectivity for mono N-benzylation, but in these cases steric control was exerted by an asymmetric bisaminal bridge and not by C-functionalisation at the 6-position of the macrocycle backbone.[10a,b] Removal of the bisaminal bridge was achieved quantitatively by acid hydrolysis under mild conditions to yield the C- and N-substituted macrocycle, **5**.[5] Furthermore, **5** can be considered a useful precursor to tri-N-substitution. After derivatisation of the remaining three secondary amines of the macrocycle, the benzyl group can easily be removed by hydrogenolysis.[14]

If di- or tetra-N-substitution of the C-functionalised macrocycle is required, then the bisaminal bridge of **3** can be removed to afford 6-(4-nitrobenzyl)-1,4,8,11-tetraazacyclotetradecane, **6** (i.e., C-functionalised cyclam), in excellent yield (>90%).[5] In the procedures published to date, C-functionalisation at the 6-position was introduced by heating a mixture of the appropriate malonate derivative and the linear tetraamine, *N*,*N*-bis(2-aminoethyl)-1,3-propanediamine to reflux in ethanol to give a cyclic diamide, which was then subsequently reduced with borane in tetrahydrofuran.[12a,15] In comparison with this time-consuming (13–18 d) and low-yielding (ca. 20%) strategy for the synthesis of **6** or its 4-cyanobenzyl analogues, the scheme described herein is far more efficient. The two key steps, that is cyclisation followed by bisaminal bridge removal, result in formation of **6** in good overall yield (67%) and after a total reaction time of only 8 d. Tetra-N-substitution of **6** is straightforward, typically involving addition of an excess of the appropriate alkyl halide compound to a solution of the macrocycle.[15] In order to achieve di-N-substitution however, **6** can be condensed with glyoxal in cold acetonitrile to give bisaminal, **7**, quantitatively.[16] It is well established that on reaction of glyoxal with cyclam, only the *cis*-diastereoisomer is obtained.[14] As detailed earlier with respect to **3**, C-functionalisation at the 6-position gives rise to two possible diastereoisomers in which the bisaminal bridge is in the *cis*-configuration (Scheme 2c). Unlike **3**, where only one diastereoisomer exists in solution, the ^1H and ^{13}C NMR spectra of **7** exhibit two sets of signals, in approximately 1:1 ratio, indicating the formation of both diastereoisomers (**7a** and **7b**) in approximately equal amounts. The single-crystal X-ray structure (Scheme 2b) of **7a** was obtained, showing the 4-nitrobenzyl moiety in position R^3, as in **3**. A comparison of the N2–N4 distance across the macrocyclic ring revealed a slight compression in **3** relative to **7a**, attributed to the steric influence of the methyl groups (3.038(7) Å for **3** and 3.142(8) Å for **7a**).

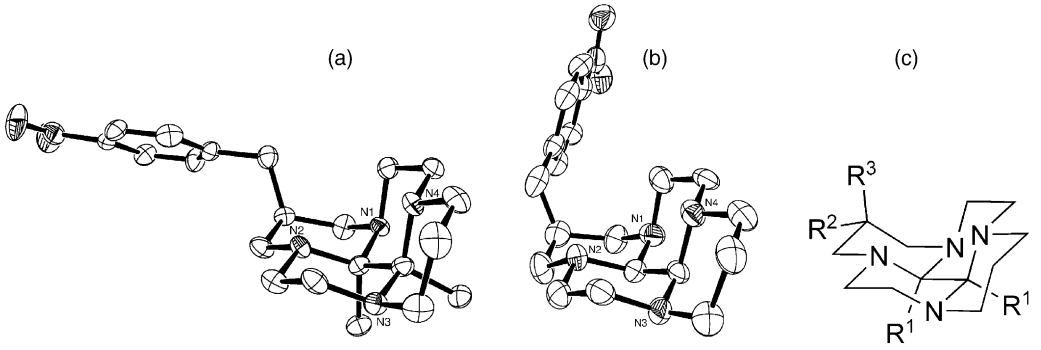
Weisman and co-workers have demonstrated that the bisaminal obtained from condensation of glyoxal with cyclam undergoes highly regioselective di-N-functionalisation and that the substitution pattern is dictated by the macrocycle conformation.[14] It follows that very similar reactivity towards electrophiles will be observed using the C-functionalised bisaminal analogue, **7**. After stirring **7** with an excess of benzyl bromide (ca. 10 equiv) for 14 d, highly regioselective di-N-substitution at non-adjacent N positions was achieved to give **8** (60%).[17] Furthermore, Weisman and co-workers have developed a series of 'cross-bridged' macrocycles by reduction of the bisaminal bridge.[14] Potentially, **8** can be used as a precursor in the formation of novel C-functionalised 'cross-bridged' macrocycles and experiments are in progress to probe this. Conversely, in a similar manner to **3** and **4**, the bisaminal bridge of **8** can easily be removed by acid hydrolysis to yield the C- and di-N-functionalised cyclam macrocycle, **9**.[5]

In summary we have shown that bisaminal methodology can be utilised effectively for the preparation of C- and N-functionalised cyclam macrocycles. The synthetic strategy not only offers a more efficient pathway to the cyclisation step but also incorporates synthons that provide convenient routes to controlled N-substitution.

Supplementary material: Crystallographic data (excluding structure factors) for the structures in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 227998 and 227999. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).



Scheme 1. Reagents and conditions:[11] (i) NaH, DME, rt, 1 h, N_2; (ii) BH_3SMe_2, THF, reflux, 3 d, N_2; (iii) PBr_3, pyridine (cat.), rt, o/n, 90–100 °C, 1 h; (iv) 10 equiv K_2CO_3, CH_3CN, 60 °C, 5 d, N_2; (v) 10% HCl/H_2O, EtOH, 60 °C, 3 d; (vi) 40% aq glyoxal, MeOH, −5 °C, 2 h, rt, 3 h; (vii) 10 equiv benzyl bromide, CH_3CN, rt, 3 d; (viii) 10 equiv benzyl bromide, CH_3CN, rt, 14 d.



Scheme 2. Reagents and conditions: (a) ORTEP plot of the single-crystal X-ray crystal structure of **3** where: R^1=CH_3, R^2=H, R^3=4-nitrobenzyl; (b) ORTEP plot of the single-crystal X-ray crystal structure of **7a** where: R^1=H, R^2=H, R^3=4-nitrobenzyl; (c) general schematic: R^1=H, CH_3; R^2=H, R^3=4-nitrobenzyl or R^2=4-nitrobenzyl, R^3=H.

Acknowledgements

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17. Efforts to compare reactivity of **7a** and **7b** are in progress.