Efficient syntheses of polymerisable pendant arm azamacrocycles and formation of poly(vinylbenzyltriazacyclododecane)

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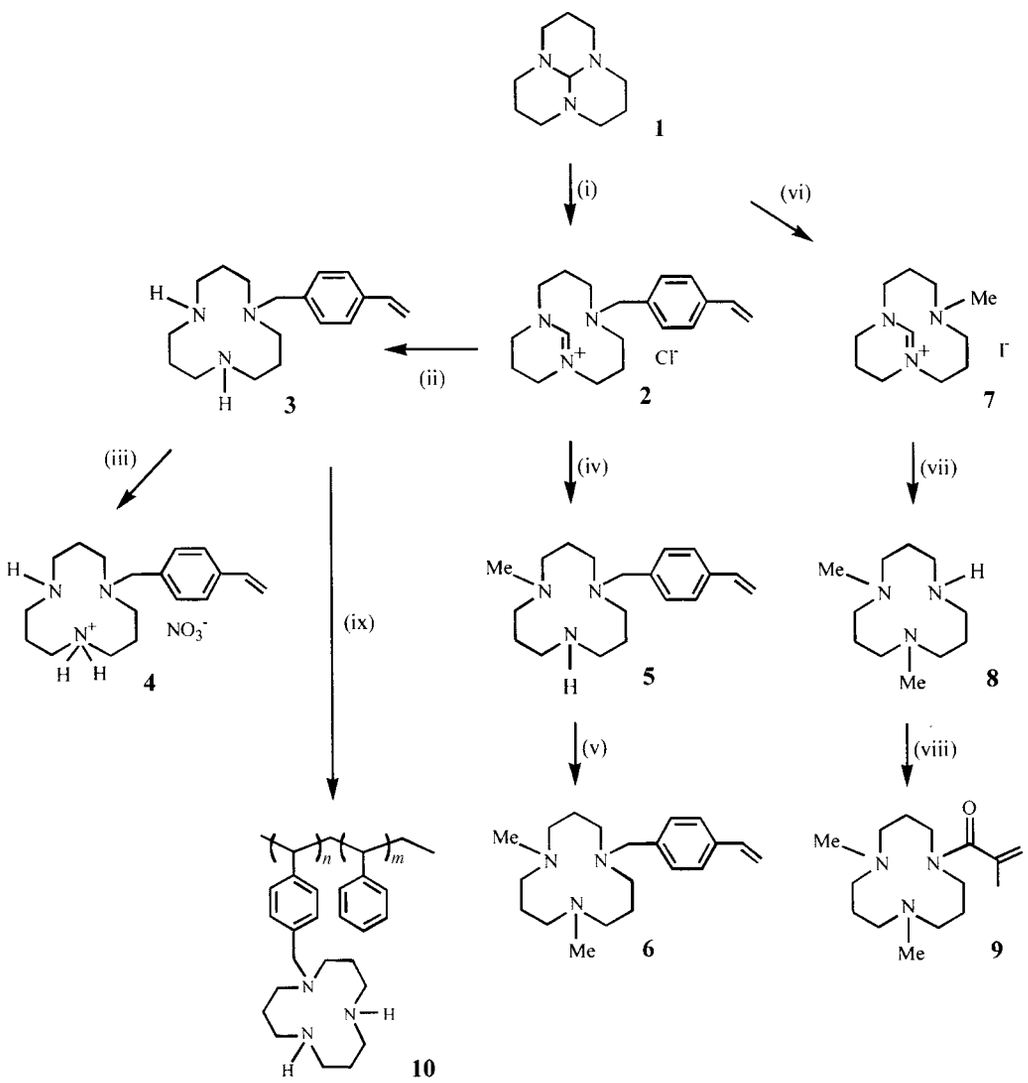
Synthetic routes to a number of metal-free triazacyclododecane derivatives featuring the unsymmetrical incorporation of polymerisable pendant side arms such as vinylbenzene and methacrylate have been developed; the structure of a nitrate salt of the vinylbenzene-substituted species has been determined by single crystal X-ray diffraction and the first polymer-bound triazamacrocycles formed *via* free-radical polymerisation of a metal-free macrocycle-containing monomer.

The importance and chemistry of azamacrocycles is well-known[1] and continues to be of topical interest. However, to selectively functionalise these derivatives is not straightforward due to synthetic difficulties and although in recent years elegant syntheses have been developed to tackle this,[2,3] there is much scope for further development. Our aim has been to establish versatile and efficient synthetic routes to pendant arm macrocycles, focusing on polymerisable pendant arms thus leading to novel metal-free or metal-ion containing polymers by polymerisation of the macrocyclic monomers or copolymerisation with monomers such as styrene. It is thought that the chemical and physical properties will be changed by metal ion substitution but also that the materials may act as anchors for metal complex assisted catalysis and as polymer-supported metal ion filters.[4] This is an active area of interest with many applications possible, particularly environmental. For example, recent work has involved polymerisation of metal-ion containing monomers featuring 1,4,7-triazacyclononane, the demetallated product being highly selective for Cu^{2+} ions,[5] oligonucleotide-tethered 1,5,9-triazacyclododecanes[6] and novel thiacrown polymers for extraction of Hg.[7]

The Richmann–Atkins cyclisation[8] has been the standard route for the formation of azamacrocycles and utilises tosyl protecting groups. However, complete removal of these groups following cyclisation is difficult and overall yields are variable, featuring unwanted monotosylated products. The use of a central fragment to protect nitrogen atoms from secondary electrophilic attack allows formation of monosubstituted triazamacrocycles. The intermediate triazatricyclo[7.3.1.0^{5,13}]-tridecane **1** can be synthesised by the routes of Alder[9] or Haseltine.[10] We have taken this intermediate and further demonstrated its versatility. To date, **1** has generally been treated with bromo or iodo reagents, but we have found that with modification of the reaction conditions, cheaper and more readily available chloro-reagents can be used. Thus, addition of vinylbenzyl chloride to a hexane solution of **1** followed by stirring at 60 °C gives the amidinium species **2** in 76% yield. This can be converted to the free amine-substituted macrocycle, 1-(4-vinylbenzyl)-1,5,9-triazacyclododecane **3** by addition of 0.75 M NaOH in a water–ethanol mixture (2:1) with prolonged refluxing (94%) (Scheme 1).† By way of purification and crystallisation, this fairly unstable species was treated with 1 equiv. of dilute HNO_3 quaternising one N atom and forming a crystalline nitrate salt **4**. After recrystallisation from methanol, this was subjected to X-ray crystal analysis; structures of metal-free substituted azamacrocycles are rare due to solvent inclusion, hydrolysis or the oily/non-crystalline nature of many of the products.[2] The X-ray analysis of **4**‡ shows the macrocycle to have a typically folded geometry (Fig. 1) with the nitrogen lone pairs on N(1) and N(5), and one of the protons on N(9), directed into the ring centre. The conformation is stabilised in part by an intramolecular N–H···N hydrogen bond (**a** in Fig. 1) between the quaternary nitrogen centre N(9) and N(5); the contact to the other ring nitrogen N(1) is significantly longer and probably only constitutes a weak interaction. The other ammonium hydrogen atom is hydrogen bonded to the nitrate anion (**b** in Fig. 1). The assignment of the cationic centre as N(9) rather than N(5) was based on an unambiguous location of all of the amino hydrogen atoms.

Methylation of the N atoms by the Eschweiler–Clarke reductive alkylation using formaldehyde is a common procedure. However, this can lead to cleavage of the macrocycle[11] and we have found formation of a mixture of methylated species, but here the use of sodium borohydride can alleviate these problems. From **2**, the monomethyl derivative **5** can be formed almost exclusively in 84% yield using $NaBH_4$ in ethanol.§ Alder has communicated[9] a dimethylated derivative **8** but with only limited experimental details and spectral characterisation and we have used a variation of this procedure. Thus, addition of 37–40% aqueous formaldehyde to **5** in methanol, followed by $NaBH_4$, gives the dimethylated **6** in 70 yield.§ Similarly, the amidinium precursor **7** and $NaBH_4$ are combined to form **8** in 60% yield *via* reductive alkylation. This clean and efficient route could lead to a range of unsymmetrically multi-substituted species, a potentially important development. To incorporate a further polymerisable pendant side arm, a CH_2Cl_2 solution of methacryloyl chloride can be added to **8** in CH_2Cl_2 at 0 °C and then allowed to warm to room temperature. Washing with NaOH solution and CH_2Cl_2 extraction of the product gives **9** in 74% yield.§

Initial polymerisation studies have featured the polymerisation of the free triazacyclododecane ligand **3** with the radical initiator AIBN [2,2′-azobis(2-methylpropionitrile)] or co-polymerisation with various amounts of styrene to form the first metal-free polymer-bound triazamacrocyclic system (Fish *et al.*[5] have recently reported polymerisation of a similar Zn-bound macrocyclic system but stated that efforts to prepare the untemplated polymer *via* co-polymerisation failed, with no polymeric material formed, this being apparently due to the unique role of the metal ion template in the kinetics of the polymerisation process). Polymerisations have generally been carried out in methanol but polymers with a high percentage of macrocycle have poor solubilities in aprotic solvents. However, when 1% of the macrocycle was used, the polymers are highly



Scheme 1 *Reagents and conditions*: i, 4-vinylbenzyl chloride, hexane, 60 °C, 48 h (76%); ii, 0.75 M NaOH, water–ethanol (2 : 1), 72 h (94%); iii, dil. HNO_3 (1 equiv.) (70%); iv, ethanol, $NaBH_4$, 0 °C, then reflux, 8 h (84%); v, methanol, formaldehyde (37–40%), $NaBH_4$, stir, rt, 12 h (70%); vi, MeI, CH_2Cl_2, N_2 24 h (85%); vii, ethanol, $NaBH_4$, N_2, reflux, 12 h (60%); viii, CH_2Cl_2, methacryloyl chloride, 0 °C, then stir, rt, 1 h (74%); ix, styrene (99 equiv.), AIBN, methanol, stir, 6 h (21%).

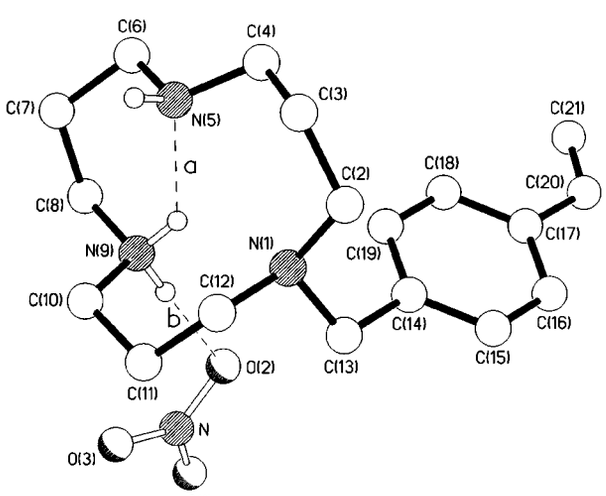


Fig. 1 The molecular structure of **4**. Selected bond lengths (Å); N(1)–C(2) 1.472(3), N(1)–C(12) 1.473(3), N(1)–C(13) 1.467(3), N(5)–C(4) 1.457(4), N(5)–C(6) 1.465(4), N(9)–C(8) 1.492(4), N(9)–C(10) 1.484(3), C(20)–C(21) 1.297(5). The hydrogen bonding geometries are [N · · · N], [H · · · N] (Å), [N–H · · · N] (°); **a**) 2.73, 2.03, 134 and **b**) 2.91, 2.02, 173.

soluble in chlorocarbon solvents and for **10**, GPC data show $M_w = 7530$, $M_n = 4660$, polydispersity = 1.6 (GPC data are expressed as calibrated by polystyrene).

Further on-going studies feature the metal complexation of these species, incorporation of different side arms and further polymerisation of metal-free and metal-templated monomers.

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Notes and references

† All the compounds exhibited spectral data consistent with their structures.

‡ *Crystal data for* **4**: $[C_{18}H_{30}N_3][NO_3]$, $M = 350.5$, monoclinic, $P2_1/c$ (no. 14), $a = 9.382(2)$, $b = 12.135(1)$, $c = 17.121(2)$ Å, $\beta = 97.22(1)°$, $V = 1933.7(5)$ Å^3, $Z = 4$, $D_c = 1.204$ g cm^{-3}, μ(Mo-Kα) = 0.83 cm^{-1}, $F(000) = 760$, $T = 293$ K; clear blocks, 0.90 × 0.43 × 0.37 mm, Siemens P4/PC diffractometer, ω-scans, 3408 independent reflections. The structure was solved by direct methods and the non-hydrogen atoms refined anisotropically using full matrix least-squares based on F^2 to give $R_1 = 0.052$, $wR_2 = 0.121$ for 2203 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta \leq 50°$] and 239 parameters. CCDC reference number 207/328. See http://www.rsc.org/suppdata/p1/1999/1621 for crystallographic files in .cif format.

§ Reaction conditions for the preparation of **5**: **2** (1.36 g, 4.1 mmol) was dissolved in ethanol (50 mL) and cooled in an ice-bath. Sodium borohydride (1.6 g, 41 mmol) was added with stirring and the reaction flask was removed from the ice-bath. After 1 h the mixture was heated to

reflux for a further 8 h. The slush was allowed to cool then added to diethyl ether (500 mL) and placed in a freezer for 2 h, then filtered. To the ethereal solution was added concentrated hydrochloric acid forming a white precipitate, which was separated and dissolved in water (150 mL). Sodium hydroxide pellets were added until pH ≈ 14. The aqueous solution was extracted with dichloromethane (4 × 50 mL portions) and the combined organic layers were dried over magnesium sulfate and the solvent was removed *in vacuo* to give a pale yellow oil (1.0 g, 3.4 mmol). Yield 84%. ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.45–1.81 (m, 6H, $CH_2CH_2CH_2$), 2.19 (s, 3H, NCH_3), 2.37 (t, 2H, NCH_2CH_2, ^3J 5.8), 2.41–2.51 (m, 4H, NCH_2CH_2), 2.56 (t, 2H, NCH_2CH_2, ^3J 5.6), 2.62 (t, 2H, NCH_2CH_2, ^3J 5.0), 2.83 (t, 2H, NCH_2CH_2, ^3J 5.0), 3.41 (s, 2H, $NCH_2C_6H_4$), 5.19 (ABX, 1H, -HC=CH_AH$_B$, $^3J_{AX}$ 10.9, $^2J_{AB}$ 1.0), 5.70 (ABX, 1H, -HC=CH$_B$H, $^3J_{BX}$ 17.6, $^2J_{AB}$ 1.0), 6.67 (ABX, 1H, -HC=CH$_2$, $^3J_{AX}$ 10.9, $^3J_{BX}$ 17.6), 7.23–7.37 (m, 4H, C_6H_4); ^{13}C {^{1}H} NMR (67.5 MHz, $CDCl_3$) δ 23.8 ($CH_2CH_2CH_2$), 24.0 ($CH_2CH_2CH_2$), 24.2 ($CH_2CH_2CH_2$), 40.7 (NCH_3), 48.5 ($RHNCH_2CH_2$), 49.5 ($RHNCH_2CH_2$), 50.2 ($RR'NCH_2C_6H_6$), 54.3 ($RR'NCH_2CH_2$), 54.5 ($RR'NCH_2CH_2$), 57.4 (-(H_3C)NCH_2CH_2), 58.7 (-(H_3C)NCH_2CH_2), 113.6 (H_2C=CH-C_6H_4), 126.3 (C_6H_4), 129.0 (C_6H_4), 136.5 (C_6H_4), 136.6 (H_2C=CH-C_6H_4), 139.1 (C_6H_4); MS (CI +ve [NH_4]) 226 [100, $(M + H)^+$], 184 [50, $C_{10}H_{22}N_3^+$].

For **6**: **5** (1.0 g, 3.4 mmol) was dissolved in methanol (25 mL) then 37–40% aqueous formaldehyde (2.5 mL) was added and stirred for 2 min. Sodium borohydride (1.4 g, 37 mmol) was added rapidly and the mixture stirred for 12 h. The reaction mixture was added to diethyl ether (250 mL), and cooled to −20 °C for 3 h after which the white precipitate was filtered and the filtrate was extracted with 10% hydrochloric acid solution. The aqueous solution was brought to pH ≈ 14 by addition of sodium hydroxide pellets and extracted with dichloromethane (3 × 10 mL), the combined organic fractions were dried over magnesium sulfate, filtered and the solvent was removed *in vacuo* to give a clear oil that solidified on standing (0.76 g, 2.4 mmol). Yield 70%. ^{1}H NMR (270 MHz, 343 K, $C_6D_5CD_3$) δ 1.39–1.56 (m, 6H, $CH_2CH_2CH_2$), 2.07 (s, 6H, NCH_3), 2.28 (t, 4H, NCH_2CH_2, ^3J 3.1), 2.38 (t, 4H, NCH_2CH_2, ^3J 2.8), 2.56 (t, 4H, NCH_2CH_2, ^3J 5.4), 3.43 (s, 2H, $NCH_2C_6H_4$), 5.05 (ABX, 1H, -HC=CH_AH$_B$, $^3J_{AX}$ 10.9, $^2J_{AB}$ 1.1), 5.59 (ABX, 1H, -HC=CH$_B$H, $^3J_{BX}$ 17.7, $^2J_{AB}$ 1.1), 6.60 (ABX, 1H, -HC=CH$_2$, $^3J_{AX}$ 10.8, $^3J_{BX}$ 17.8), 7.22–7.31 (m, 4H, C_6H_4); ^{13}C {^{1}H} NMR (67.5 MHz, $CDCl_3$) δ 22.0 ($CH_2CH_2CH_2$), 22.3 ($CH_2CH_2CH_2$), 43.2 (NCH_3), 49.3 (NCH_2CH_2), 52.5 (NCH_2CH_2), 58.9 (NCH_2CH_2), 113.2 (H_2C=CH-C_6H_4), 126.0 (C_6H_4), 129.0 (C_6H_4), 136.2 (C_6H_4), 136.8 (H_2C=CH-C_6H_4), 140.3 (C_6H_4); MS (CI +ve[NH_4]) 316 [100, (M + H)].

For **9**: **8** (0.38 g, 1.9 mmol) was dissolved in dichloromethane (10 mL) and stirred at 0 °C. Methacryloyl chloride (0.2 g, 1.9 mmol) in dichloromethane (10 mL) was then added dropwise. The solution was left stirring for 1 h and allowed to reach room temperature. The solution was washed with sodium hydroxide solution (10 mL, pH ≈ 14), which was then extracted with dichloromethane (3 × 5 mL). The combined extracts were dried over sodium sulfate, filtered and dried *in vacuo* to give a clear oil (0.37 g, 1.4 mmol). Yield 74%. ^{1}H NMR (270 MHz, 378 K, $C_6D_5CD_3$) δ 1.36 (br pentet, 2H, $CH_2CH_2CH_2$), 1.55 (pentet, 4H, $CH_2CH_2CH_2$, ^3J 5.0), 1.86 (t, 3H, H_3C-C, ^4J 1.24), 1.93 (s, 6H, NCH_3), 2.16 (br t, 4H, NCH_2CH_2, ^3J 4.5), 2.24 (br t, 4H, NCH_2CH_2, ^3J 5.6), 3.50 (br t, 4H, CH_2CH_2NC=O, ^3J 7.0), 4.87 (q, 2H, H_2C=C, ^4J 1.24); ^{13}C {^{1}H} NMR (67.5 MHz, 378 K, $C_6D_5CD_3$) δ 20.2 (H_3CC=CH_2), 24.8 ($CH_2CH_2CH_2$), 25.5 ($CH_2CH_2CH_2$), 40.8 (NCH_2CH_2), 50.7 (NCH_2CH_2), 55.3 (NCH_3), 112.5 (C=CH_2), 142.6 (H_2C=C), 171.5 (C=O); MS (CI +ve [NH_4]) 268 [100, $(M + H)^+$].

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