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A Novel Method for Functionalising Resorcinarenes

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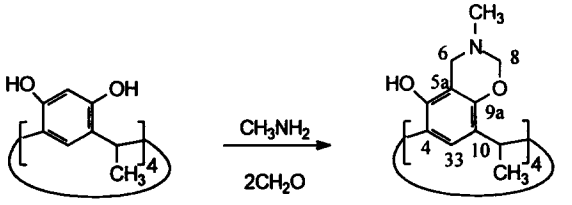
Abstract: Tetra-*N*-methyl(2-hydroxynaphthylmethyl)aminomethyl resorcinarene **5** has been synthesised either from tetrabenzoxazine resorcinarene **2** and 2-naphthol or from the C-methyl resorcinarene **1** and naphthoxazine **6**. Reaction of the tetrabenzoxazine resorcinarene **2** with C-methyl resorcinarene **1** is proposed to give carceplex **7**.

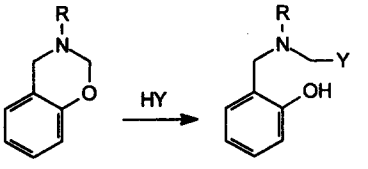
Keywords: Oxazines, resorcinarenes, carceplex.

Resorcinarene **1** is easily obtained as the all-*cis* isomer from acid-catalysed condensation of resorcinol with acetaldehyde.[1] Obvious sites for chemical modification of resorcinarene **1** are the phenolic hydroxyl groups and the *ortho*-positions of the resorcinol units. Condensation of resorcinarene **1** with methylamine and an excess of formaldehyde according to Matsushita and Matsui [2] leads to the tetrabenzoxazine derivative **2** (Scheme 1); we have confirmed the structure of **2**, and its cone conformation, by X-ray crystallographic analysis.[3]



1 Scheme 1 **2**

It is known that simple benzoxazines **3** can aminoalkylate a variety of compounds HY characterised by the presence of a highly nucleophilic carbon atom or nitrogen atom, to give tertiary amines **4** (Scheme 2).[4]



3 Scheme 2 **4**

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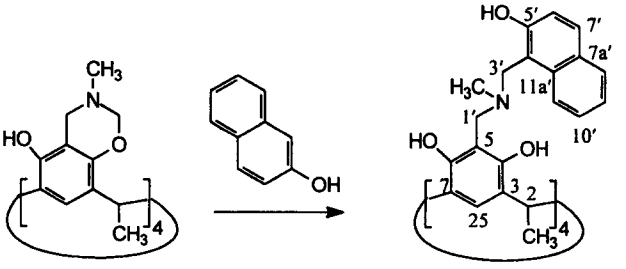
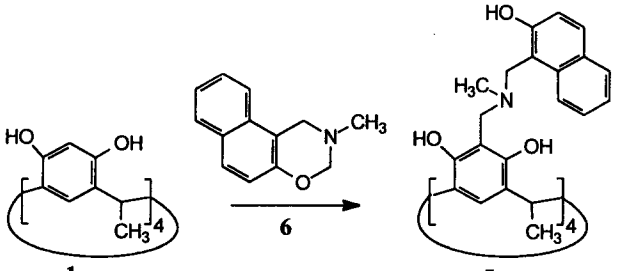
Phenols, indoles, carbazole, imides and aliphatic nitro compounds have been suggested to be suitable compounds HY. To our knowledge, however, aminoalkylation reactions involving resorcinarenes have not been reported. We now communicate a new method for the preparation of functionalised resorcinarenes. It was anticipated that benzoxazine rings subtended from a macrocyclic framework might aminoalkylate 2-naphthol. Accordingly (Scheme 3), 2-naphthol (4 mmol) was added to a solution (1 mmol) of the



2 Scheme 3 5

tetrabenzoxazine resorcinarene **2** (1.0 mmol) in ethanol:benzene (1:1) at room temperature. After several hours a precipitate separated, which was collected by filtration after 12 h and washed with ethanol and then dichloromethane. This material was determined to be the tertiary tetraamine resorcinarene **5** by IR, NMR and elemental analysis.[5] Although the required molecular ion (M_r 1342) could not be detected using FAB^+ mass spectrometry, a series of fragment ions is consistent with the proposed structure. In particular, cleavage of the *N*-methyl(2-hydroxynaphthyl)aminomethane appendages ($C_{12}H_{13}NO$) from the molecular ion to give ions at *m/z* 1154, 779 and 592 is characteristic. Moreover, the ^1H and ^{13}C NMR spectra of **5** were assigned completely by a combination of short-range and long-range 2D experiments. Only a single set of signals is observed in the ^1H NMR spectrum, suggesting that **5** also prefers a cone conformation.

Since the two *meta* hydroxy groups on each arene in **1** render the four *ortho* positions electron rich, these highly nucleophilic sites can be utilised to aminoalkylate the perimeter of the resorcinarene ring using reactant pairing complementary to that shown in Scheme 2. Thus, treatment of a solution of the C-methyl resorcinarene **1** (1.0 mmol) in ethanol:benzene (1:1) with the naphthoxazine **6** (4.0 mmol) also resulted in precipitation of the tetraamine resorcinarene **5** (Scheme 4).



1 6 Scheme 4 5

Carceplexes are closed surface compounds that permanently entrap guest molecules or ions within their shell, such that escape of the guest can occur only by rupture of covalent bonds. A novel route to a carceplex[6,7,8,9,10] may be available by extension of our results, from reaction of the resorcinarene **1** with the tetrabenzoxazine resorcinarene **2**.* The formation of a carceplex by such a new and direct method would be important since the synthesis of such macrocycles usually requires multi-step sequences.

Acknowledgement

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References and Notes

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2. Y. Matsushita, T. Matsui, *Tetrahedron Lett.*, 1993, **34**, 7433-7436.
3. Spectral data for **2**: 15H,23H,26H,31H-6,32:8,14,22:24,30-tetrametheno-2H,7H,10H,18H-cyclotetracosa[1,2-e:7,8-e':13,14e'':19,20e''']tetrakis[1,3]oxazine-5,13,21,29-tetraol-3,11,19,27-tetramethyl-3,4,11,12,19,20,27,28-octahydro-7,15,23,31-tetramethyl(7R*,15R*,23R*,31R*)octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26)21,23-dodecane, 55%, colourless cubes from chloroform/acetone, m.p. >300 °C (dec. >180). (Found: M+H$^+$; 765.3886, $C_{44}H_{53}N_4O_8$. Calc.: 765.3864). IR ($CDCl_3$) ν_{max} 3294, 1598, 1231, 1101, 958 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ_{ppm} 1.75 (d, *J* 7.2, 12H, $4CH_3$), 2.52 (s, 12 H, $4NCH_3$), 3.75, 3.91 (2d, *J* 17.3, 8H, H-6,14,22,30), 4.51 (q, *J* 7.3, 4H, H-3,11,19,27), 4.80, 4.86 (2d, *J* 9.5, 8H, H-8,16,24,32), 7.26 (s, 4H, H-33,34,35,36), 7.79 (s, exchanges with D_2O, 4H, 4OH). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_{ppm} 19.8 4(CH_3), 27.0 4(CH), 40.0 4(NCH_3), 48.2 (C-5,13,22,29), 85.5 (C-8,16,24,32), 108.2 (C-5a,13a,21a,29a), 120.8 (C-33,34,35,36), 124.5 (C-2,10,18,26), 125.2 (C-4,12,20,28), 147.2 (C-1a,9a,17a,25a), 149.4 (C-5,13,22,29). FAB$^+$ mass *m/z* 765 (M+H, 2%), 721 (M-$CH_3N{=}CH_2$, 2), 678 (721-$CH_3N{=}CH_2$, 2), 635 (678-$CH_3N{=}CH_2$, 4), 592 (635-$CH_3N{=}CH_2$, 2).
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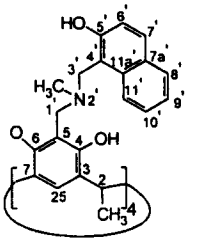
5. Data for **5**: 4,6,10,12,16,18,22,24-Octahydro-2,8,14,20-tetramethyl-5,11,17,23-tetrakis-(*N*-methylaminomethy)-2-naphthol)methyl[19.3.1.1^{3,7}1^{9,13}1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecane, pale pink solid (69%), m.p. >340 °C. (Found: C, 71.58; H, 6.07; N, 4.27, $C_{84}H_{84}N_4O_{12}{\cdot}CH_2Cl_2$. Calc.: C, 71.57; H, 6.08; N, 3.93 %). IR ($CDCl_3$) ν_{max} 3235, 1607, 1516, 1219 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6, 30 °C) δ_{ppm} 1.56 (d, *J* = 7.0Hz, 12H, $4CH_3$), 2.12 (s, 12H, $4NCH_3$),

3.79(s, 8H, 4H-1'), 4.16 (s, 8H, 4H-3'),4.25 (q, J = 7.0Hz, 4H, 4CHCH$_3$), 7.23 (d, J = 8.9 Hz, 4H, 4H-6'), 7.27 (s, 4H, H-25,26,27,28), 7.39 (t, J = 7.4 Hz, 4H, 4H-10'), 7.79 (d, J = 8.9 Hz, 4H, 4H-7'), 7.85 (d, J = 8.0 Hz, 4H-8'), 7.99 (d, J = 8.4 Hz, 4H, 4H-11'). ^{13}C-NMR (100 MHz, DMSO-d$_6$, 30 °C) δ_{ppm} 19.3 4(CH_3), 27.4 4(NCH_3) 40.1 4(CH), 50.3 4(C-1'), 53.6 4(C-3'), 107.3 (C-5,11,17,23), 113.0, 4(C-4'), 117.9 4(C-6'), 121.9 (C-25,26,27,28), 122.4 4(C-11'), 122.6 4(C-9'), 124.2 (C-1,3,7,9,13,15,19,21), 126.7 4(C-10'), 128.0 4(C-7a'), 128.4 4(C-8'), 129.6 4(C-6'), 133.5 4(C-11a'), 150.6 (C-4,6,10,12,16,18,22,24), 154.3 4(C-5'). FAB$^+$ mass *m/z* 1342 (M, 1%), 1154 (M-H-$C_{12}H_{13}NO$, 1), 998 (1154-$C_{11}H_8O$, 1), 779 (966-$C_{12}H_{13}NO$, 4), 592 (779-$C_{12}H_{13}NO$,2).



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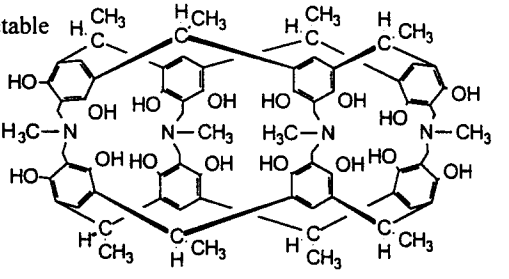
*Equimolar reaction between **1** and **2** under high dilution in ethanol-benzene (1:1) resulted in the precipitation of a pale orange product (76%) within minutes. Due to the characteristic[6] insolubility of this compound, NMR spectroscopy was not possible. Although mass spectrometry did not reveal the molecular ion (M 1300), the compound clearly is neither the resorcinarene **1** nor the tetrabenzoxazine resorcinarene **2** since the molecular ion for each starting material was detectable under FAB$^+$ ionization. The poor solubility, in tandem with our demonstration that the tetrabenzoxazine resorcinarene **2** readily aminoalkylates electron-rich arenes, provides strong presumptive evidence that the product is the carceplex **7**.



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