Synthesis of Calix[4]pyrrole-Based Acrylate and Acrylamide Monomers: Precursors for Preparation of Anion-Selective Polymer Membranes

Grigory V. Zyryanov, Thomas H. Kinstle, Pavel Anzenbacher, Jr.*

Department of Chemistry and Center for Photochemical Sciences, Bowling Green State University, Bowling Green, OH 43403, USA
Fax +1(419)3722080; E-mail: pavel@bgsu.edu

Received 18 December 2007

Abstract: Octamethylcalix[4]pyrrole derivatives with hydroxy alkyl and amino alkyl side chains were prepared and converted into the corresponding acrylate and acrylamide derivatives, respectively.

Key words: calix[4]pyrrole, macrocycle, acrylate, acrylamide, receptor, polymer

Recent interest in supramolecular chemistry of anions led to the development of numerous receptors and sensors capable of anion binding and sensing.[1] Among the successful receptors for anions, the octamethylcalix[4]pyrrole (**1** (OMCP, Figure 1), a compound first synthesized by Bayer[2] and rediscovered by Sessler,[3] achieved wide recognition as a receptor for halides such as fluoride or chloride and, to a lesser extent, also for carboxylates and phosphates.[4]

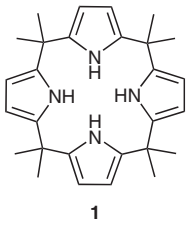


Figure 1

Recent discoveries suggest potential utility of OMCP derivatives in hydrophilic polymer matrices for binding and sensing of anions in aqueous environments.[4,5] For the purpose of preparation of polymer membranes with covalently embedded OMCP receptors, we have synthesized several polymerizable OMCPs with multiple acrylate or acrylamide moieties to serve as cross-linking co-monomers in the preparation of polymeric membranes capable of binding and potentially also extracting/sequestering anions at the water–polymer interface (Figure 2). In the design of polymerizable calixpyrroles **2**–**4** we decided to incorporate multiple polymerizable moieties since in the previous materials utilizing calixpyrroles with only one acrylate connection to the polymer backbone resulted in materials that displayed certain degradation when exposed to basic aqueous anion solutions. Particularly, the tetraamide **4** is expected to circumvent potential problems associated with hydrolysis of ester linkages.

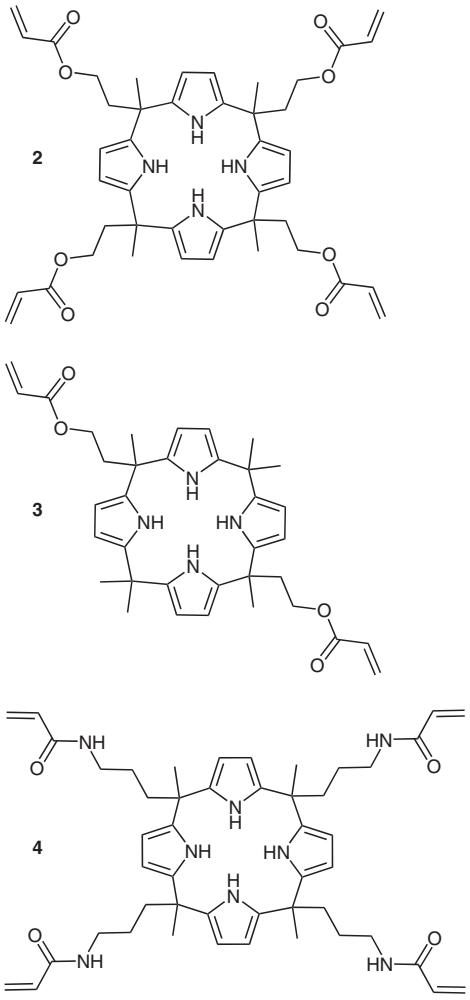
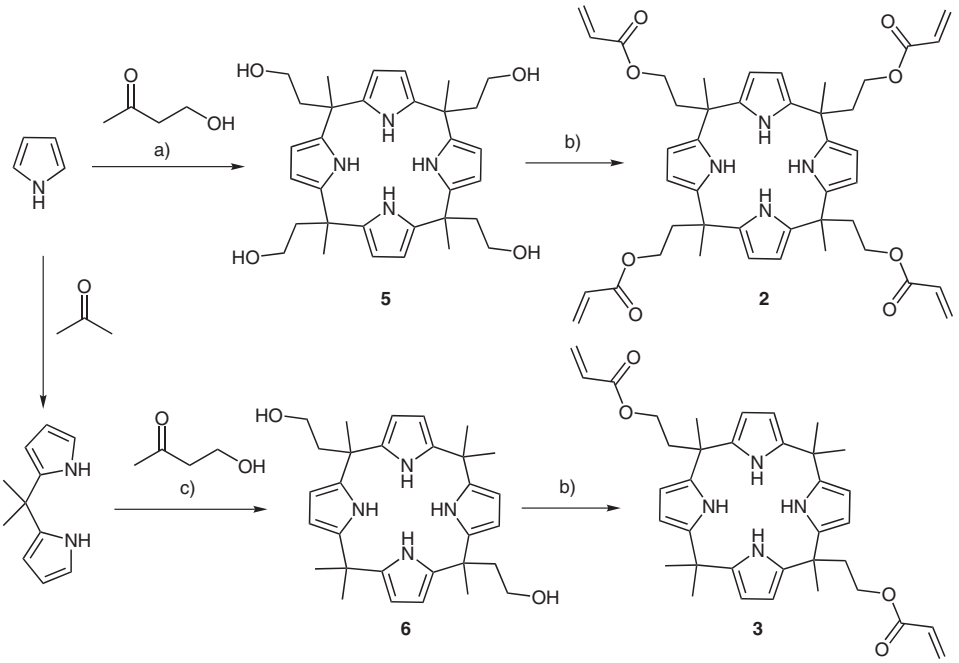


Figure 2

The acrylate calixpyrroles **2** and **3** were prepared according to Scheme 1.[6,7] Briefly, pyrrole and 4-hydroxybutan-2-one were condensed in the presence of HCl to yield the tetrahydroxyethyl precursor **5**.[7] Reaction of **5** with acryloyl chloride resulted in a low yield (15%) of tetraacrylate **2**. Regardless of the temperature, base, or HCl scavenger used, a portion of the product polymerized. The polymerization may be avoided by using less reactive acylation agents such as succinimidyl acrylate to give **2** in a moderate yield (31%), while allowing starting material **5** to be recovered.

SYNLETT 2008, No. 8, pp 1171–1174
Advanced online publication: 16.04.2008
DOI: 10.1055/s-2008-1072590; Art ID: S10407ST



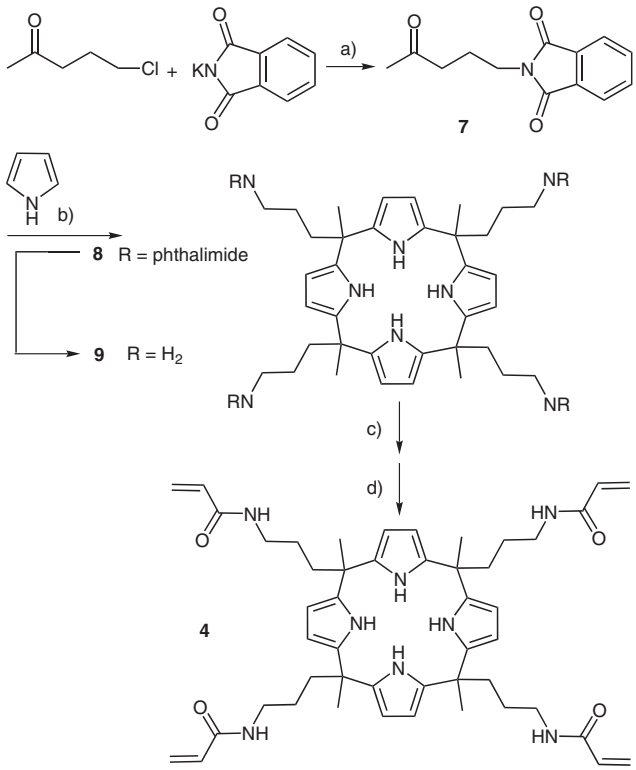
Scheme 1 *Reagents and conditions*: a) H_2O–EtOH (1:1), HCl (concd), 25 °C, 2 h, 50–60%; b) hydroxysuccinimidyl acrylate, DMF–$(i\text{-Pr})_2$NEt, 0–25 °C, overnight, 31–60%; c) MeOH, $MeSO_3H$, 25 °C, 2 h, 60%.

The synthesis of tetraacrylamide **4** was accomplished following the Scheme 2.[8] Thus, 5-chloropentan-2-one was treated with potassium phthalimide to yield 5-(*N*-phthalimidyl)pentan-2-one (**7**), which was then used to synthesize tetraphthalimide calix[4]pyrrole (**8**). Hydrazinolysis of the phthalimido moieties yielded calixpyrrole tetraamine **9**, which was then converted into the acrylamide calix[4]pyrrole **4** by the reaction with *N*-hydroxysuccinimidyl acrylate.

Interestingly, while there is an obvious possibility to configurational isomers arising from the orientation of the substituents on the *meso* carbons,[3d] the NMR spectra of alcohols **5** and **6** did not display resonances that could be attributed to configurational isomers. Only compound **8** with the four phthalimide moieties displayed broadening of the proton resonances suggesting possible isomers. It is conceivable that the substituents do not create enough difference in the magnetic environment to make the configurational isomers discernible by NMR or by chromatography. Efforts to characterize the possible isomers by X-ray crystallography are under way.

The final products **2**–**4** are reasonably stable without any stabilizer added, and may be kept in the freezer for several weeks prior to their use. Preliminary results show that the compounds **2**–**4** are useful as anion-binding cross-linkers in acrylate, methacrylate, or acrylamide polymers and copolymers.

In summary, a simple method for synthesis of polymerizable/cross-linking compounds utilizing calix[4]pyrrole receptor moieties was developed. These materials are ex-



Scheme 2 *Reagents and conditions*: a) DMF, 80 °C, 70%; b) MeOH, $MeSO_3H$, 25 °C, 3 h, 60%; c) EtOH–toluene (1:1), $N_2H_4{\cdot}H_2O$, reflux, overnight, used crude; d) DMF–$(i\text{-Pr})_2$NEt, hydroxysuccinimidyl acrylate, 0–25 °C, overnight, 25%.

pected to play an important role in the preparation of environmentally stable ion-sensitive polymer membranes for use in various anion sensors.

Acknowledgment

Support for this research from the NSF (SENSORS #0330267 to P.A., EXP-LA #0731153 to P.A., T.K.), support from the Alfred P. Sloan Foundation (P.A.), and BGSU (Technology Innovations Enhancement grant) is gratefully acknowledged. We would like to thank Lic. Manuel Palacios for helpful discussion on the topic of calix[4]pyrrole synthesis.

References and Notes

(1) (a) Sessler, J. L.; Gale, P. A.; Cho, W.-S. In *Anion Receptor Chemistry. Monographs in Supramolecular Chemistry*; RSC Publishing: Cambridge, **2006**. (b) Suksai, C.; Tuntulani, T. *Top. Curr. Chem.* **2005**, *255*, 163. (c) Martínez-Máñez, R.; Sancenón, F. *Chem. Rev.* **2003**, *103*, 4419.

(2) Bayer, A. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 2184.

(3) (a) Gale, P. A.; Sessler, J. L.; Král, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140. (b) Gale, P. A.; Sessler, J. L.; Král, V. *Chem. Commun.* **1998**, 1. (c) Gale, P. A.; Anzenbacher, P. Jr.; Sessler, J. L. *Coord. Chem. Rev.* **2001**, *222*, 57. (d) Anzenbacher, P. Jr.; Jursikova, K.; Lynch, V. M.; Gale, P. A.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 11020.

(4) (a) Nishiyabu, R.; Anzenbacher, P. Jr. *J. Am. Chem. Soc.* **2005**, *127*, 8270. (b) Nishiyabu, R.; Anzenbacher, P. Jr. *Org. Lett.* **2006**, *8*, 359. (c) Nishiyabu, R.; Palacios, M. A.; Dehaen, W.; Anzenbacher, P. Jr. *J. Am. Chem. Soc.* **2006**, *128*, 11496. (d) Palacios, M. A.; Nishiyabu, R.; Marquez, M.; Anzenbacher, P. Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7538.

(5) Anzenbacher, P. Jr.; Nishiyabu, R.; Palacios, M. A. *Coord. Chem. Rev.* **2006**, *250*, 2929.

(6) **Synthesis of 2 and 3**

Method A

To the corresponding substrate (1 mmol) and anhyd Et_3N (2.5 equiv for each hydroxy group) in anhyd CH_2Cl_2 (80 mL) at –10 °C to 0 °C under Ar, acryloyl chloride (1.1 equiv for each hydroxy group) was added dropwise over 0.5 h. The reaction mixture was stirred for another 0.5 h, warmed to r.t. and left to stir overnight. The reaction mixture was then washed with sat. $NaHCO_3$, H_2O (2 × 30 mL), dried over $MgSO_4$, and evaporated to dryness. Recrystallization from MeOH–CH_2Cl_2 or flash chromatography (SiO_2, 0–5% MeOH in $CHCl_3$) afforded the product as a white solid.

Method B

To the corresponding substrate (0.5 mmol) and anhyd (*i*-Pr)$_2$NEt (2.5 equiv for each hydroxy group) in anhyd DMF (25 mL) at –10 °C to 0 °C under Ar, the solution of *N*-hydroxysuccinimidyl acrylate (1.1 equiv for each hydroxy group) in anhyd DMF (1 mL) was added dropwise over 0.5 h. The reaction mixture was stirred for another 0.5 h, warmed to r.t. and left to stir overnight. The reaction mixture was then evaporated to dryness and diluted with CH_2Cl_2. After that the procedure is similar to method A.

Compound **2**: yield 15% (A), 31% (B); mp >200 °C (dec.). ^{1}H NMR (250 MHz, $CDCl_3$ and DMSO-d_6): δ = 2.19–2.21 (m, 8 H, CH_2), 2.44–2.50 (m, 12 H, CH_3), 3.92 (t, ^3J = 5.7 Hz, 8 H, CH_2), 5.69 (dd, *J* = 8.8, 1.3 Hz, 4 H, *cis* CH_2=CH), 5.80 (d, *J* = 2.3 Hz, 8 H), 5.95 (dd, *J* = 14.5, 8.8 Hz, 4 H, CH_2=CH), 6.23 (dd, *J* = 14.5, 1.5 Hz, 4 H, *trans* CH_2=CH), 8.23 (br s, 4 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.3, 37.7, 38.7, 61.7, 104.3, 128.6, 130.4, 136.6, 166.0. MS (MALDI-TOF): 765.54 [MH$^+$]. Anal. Calcd for $C_{44}H_{52}N_4O_8$ (764.91): C, 69.09; H, 6.85; N, 7.32. Found: C, 68.94; H, 6.88; N, 6.99.

Compound **3**: yield 29% (A), 60% (B); mp >200 °C (dec.). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.47–1.58 (m, 18 H, CH_3), 2.23–2.28 (m, 4 H, CH_2), 4.03–4.08 (m, 4 H, OCH_2), 5.80 (dd, *J* = 8.5, 1.3 Hz, 2 H, *cis* CH_2=CH), 5.90–5.95 (m, 8 H, HetH), 6.11 (dd, *J* = 14.0, 8.3 Hz, 2 H, CH_2=CH), 6.35 (dd, *J* = 15.0, 1.5 Hz, 2 H, *trans* CH_2=CH), 7.04 (br s, 4 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.5, 29.0, 30.1, 35.2, 37.6, 43.9, 61.6, 103.0, 104.0, 128.5, 130.4, 137.2, 138.7, 166.1. MS (MALDI-TOF): 596.26 [M$^+$]. Anal. Calcd for $C_{36}H_{44}N_4O_4$ (596.76): C, 72.46; H, 7.43; N, 9.39. Found: C, 72.55; H, 7.68; N, 9.11.

(7) **Synthesis of 5**

Similarly to the reported procedure,[9] to a solution of pyrrole (1.7 mL, 24 mmol) and 4-hydroxybutan-2-one (2.1 mL, 24 mmol) in 50% aq EtOH (15–20 mL), concd HCl (1–1.5 mL) was added dropwise over 1 h at r.t. under Ar. After 0.5 h a precipitate formed. The dark solution was stirred for additional 1–2 h, then filtered, and the precipitate was washed with H_2O and small amount of MeOH, dried, and recrystallized from MeOH–CH_2Cl_2 (1:1) to afford a white solid.

Synthesis of 6

To a solution of dipyrromethane[10] (1 mmol) and ketone (1 mmol) in MeOH (5 mL), MsOH (0.1 mL) was added dropwise over 0.5 h at r.t. under Ar. The dark solution was stirred until the precipitation occurred or for 2–3 h. The solution was then evaporated under reduced pressure, treated with H_2O, and the precipitate that formed was filtered off, washed with H_2O and small amount of MeOH, dried, and recrystallized from MeOH–CH_2Cl_2 (1:1) to afford a white solid.

Compound **5**: yield 50%; mp >200 °C (dec.). ^{1}H NMR (250 MHz, $CDCl_3$ and DMSO-d_6): δ = 1.39 (br s, 12 H, CH_3), 2.03–2.10 (m, 8 H, CH_2), 3.34 (t, ^3J = 5.7 Hz, 8 H, OCH_2), 5.68–5.77 (m, 8 H, HetH), 7.58 (br s, 4 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$ and DMSO-d_6): δ = 26.5, 37.5, 43.0, 58.9, 103.2, 137.44. MS (MALDI-TOF): *m/z* = 549.59 [MH$^+$]. Anal. Calcd for $C_{32}H_{44}N_4O_4$ (548.34): C, 70.04; H, 8.08; N, 10.21. Found: C, 69.94; H, 8.37; N, 9.99.

Compound **6**: yield 60%; mp >200 °C (dec.). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.50 (br s, 6 H, CH_3), 1.53 (br s, 12 H, CH_3), 2.13–2.18 (m, 4 H, CH_2), 3.58 (t, ^3J = 5.0 Hz, 4 H, OCH_2), 5.88–5.95 (m, 8 H, HetH), 7.04 (br s, 4 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6, 29.1, 29.3, 35.2, 37.5, 42.9, 59.5, 102.8, 103.8, 138.5, 139.2. MS (MALDI-TOF): *m/z* = 489.59 [MH$^+$]. Anal. Calcd for $C_{30}H_{40}N_4O_2$ (488.66): C, 73.74; H, 8.25; N, 11.47. Found: C, 74.04; H, 8.37; N, 11.79

(8) **Synthesis of 8**

To a solution of pyrrole (1 mmol) and ketone **7**[11] (1 mmol) in MeOH (5 mL), MsOH (0.1 mL) was added dropwise over 0.5 h at r.t. under Ar. The dark solution was stirred until the precipitation occurred or for 2–3 h. The solution was then evaporated under reduced pressure, treated with H_2O, and the precipitate that formed was filtered off, washed with H_2O and small amount of MeOH, dried and recrystallized from MeOH–CH_2Cl_2 (1:1) to afford a white solid of **8**.

Compound **8**: yield 59%; mp 171–173 °C (dec.). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.18–1.34 (m, 20 H, CH_2 and CH_3), 1.97–2.05 (m, 8 H, CH_2), 3.47–3.69 (m, 8 H, NCH_2), 5.83–5.97 (m, 8 H, HetH), 7.02 (br s, 2 H, NH), 7.09 (br s, 2 H, NH), 7.62–7.80 (m, 16 H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.4, 23.6, 23.9, 26.1, 26.2, 26.4, 37.3, 38.3, 38.4, 39.0, 104.0, 123.0, 123.1, 132.1, 133.6, 133.7, 133.8,

136.9, 137.1, 168.3. MS (MALDI-TOF): *m/z* = 1121.71 $[M]^+$. Anal. Calcd for $C_{68}H_{64}N_8O_8$ (1121.28): C, 72.84; H, 5.75; N, 9.99. Found: C, 72.72; H, 5.69; N, 10.12.

Tetramine 9

To a solution of compound **8** (1 mmol) in anhyd EtOH (50 mL) and anhyd toluene (50 mL), $N_2H_4 \cdot H_2O$ (10 mL, 200 mmol) was added. The clear solution was heated at reflux overnight, then allowed to cool. The precipitate that formed was filtered off. The mother liquor was evaporated to dryness to afford oily residue, which was treated with H_2O, and the precipitate that formed was filtered off, washed with H_2O, and this crude product (100% conversion according to TLC: 60% EtOAc in hexanes) was used for the next step.

Synthesis of 4

Method A

To the tetramine **9** (1 mmol) and anhyd Et_3N (10 mmol) in anhyd CH_2Cl_2 (80 mL) at –10 to 0 °C under Ar, acryloyl chloride (4.4 mmol) was added dropwise over 0.5 h. The reaction mixture was stirred for another 0.5 h, warmed to r.t. and left to stir overnight. The reaction mixture was then washed with sat. $NaHCO_3$, H_2O (2 × 30 mL), dried over $MgSO_4$ and evaporated to dryness. Flash chromatography (SiO_2, 0–5% MeOH in $CHCl_3$) afforded the product as a white solid.

Method B

To the tetramine **9** (0.5 mmol) and anhyd $(i\text{-Pr})_2NEt$ (2.1 mmol) in anhyd DMF (25 mL) at –10 to 0 °C under Ar, the solution of *N*-hydroxysuccinimidyl acrylate (2.1 mmol) in anhyd DMF (1 mL) was added dropwise over 0.5 h. The reaction mixture was stirred for another 0.5 h, warmed to r.t. and left to stir overnight. The reaction mixture was evaporated to dryness and diluted with CH_2Cl_2. After that the procedure is similar to method A.

Compound **4**: yield 10% (A), 25% (B); mp 127–129 °C (dec.). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.14–1.19 (m, 8 H, CH_2), 2.09–2.14 (m, 8 H, CH_2), 2.78–2.84 (m, 12 H, CH_3), 3.04–3.14 (m, 8 H, NCH_2), 5.71–5.77 (m, 8 H, HetH), 6.09 (dd, *J* = 8.8, 1.0 Hz, 4 H, *cis* CH_2=CH), 6.24 (dd, *J* = 14.3, 8.8 Hz, 4 H, CH), 6.61 (dd, *J* = 14.3, 1.0 Hz, 4 H, *trans* CH_2=CH), 8.60 (br s, 4 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 26.4, 37.9, 38.6, 39.8, 104.0, 126.1, 126.2, 130.8, 131.0, 136.9, 137.1, 137.3, 137.5, 165.6. MS (MALDI-TOF): *m/z* = 839.83 $[MNa^+]$. Anal. Calcd for $C_{48}H_{64}N_8O_4$ (817.07): C, 70.56; H, 7.90; N, 13.71. Found: C, 70.71; H, 7.69; N, 14.12.

(9) Soumen, D.; Kuntal, P.; Sabayasachi, S. *Tetrahedron Lett.* **2006**, *47*, 5851.

(10) Bucher, C.; Zimmerman, R. S.; Lynch, V.; Král, V.; Sessler, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 2099.

(11) (a) Sigurd, E.; Schunack, W. *Z. Naturforsch., B: Chem. Sci.* **1987**, *42*, 238. (b) Lee, C.-H.; Lee, J.-S.; Na, H.-K.; Yoon, D.-W.; Miyaji, H.; Cho, W.-S.; Sessler, J. L. *J. Org. Chem.* **2005**, *70*, 2067.