Novel synthesis and characterisation of *N*-substituted-calix[4](aza)crown derivatives

Zhi, Qiang Shi[a], Ya, Qing Feng[b]* and Shu, Xian Meng[b]

[a]*Renai College of Tianjin University, Tianjin 301636, China*
[b]*School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, P. R. China*

A novel series of calix[4](aza)crown derivatives is prepared by the reaction between calix[4](aza)crown and 4-bromoacetamido-*N*-alkyl-1, 8-naphthalimide derivatives. They may be useful fluorescent chemosensors, and have been structurally characterised by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analyses. From the analytical data, it was found those compounds adopted a cone conformation.

Keywords: calix[4]azacrown, naphthalimides, fluorescent chemosensors

The development of systems that are capable of sensing various biologically and/or chemically important negatively charged species is a research area of great importance.[1] One of the more attractive approaches in this field involves the construction of chemosensors.[2] Calix[4]azacrown derivatives are good candidates as receptors of fluorescent chemosensors, due to their binding strength and selectivity toward transition and post-transition metal ions through the three-dimensional encapsulating assistance of the appended side arm on the nitrogen atom.[3–6] On the other hand, naphthalimides are efficient fluorophores having excited state stabilities very sensitive to their substituents as well as to their surroundings.[7–10] We now report two novel calix[4]azacrown derivatives with naphthalimide groups, which may be useful fluorescent chemosensors, and the further valuation of their fluorescent activities is in progress.

From the naphthalimide **1**, via the intermediates **2a/2b** and **3a/3b** and their reaction with the crown **4** the desired products **5a** and **5b** were obtained. The structures of the compounds **5a** and **5b** were established by IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analyses. The results showed that compounds **5a–b** were in a cone conformation. Thus taking compound **5b** as an example in the ^{1}H NMR spectra in $CDCl_3$, two doublets at δ 4.12 and 3.50 ppm for the protons of the methylene bridge of the calix[4]arene skeleton indicated that compound **5b** is in a cone conformation in solution. Moreover, in the ^{13}C NMR, the signal peak of the methylene carbons of $ArCH_2Ar$ appeared at about 31 ppm in accord with the Mendoza rule.[11] It is also consistent with the cone conformation. MS and elemental analyses data further confirmed their structures.

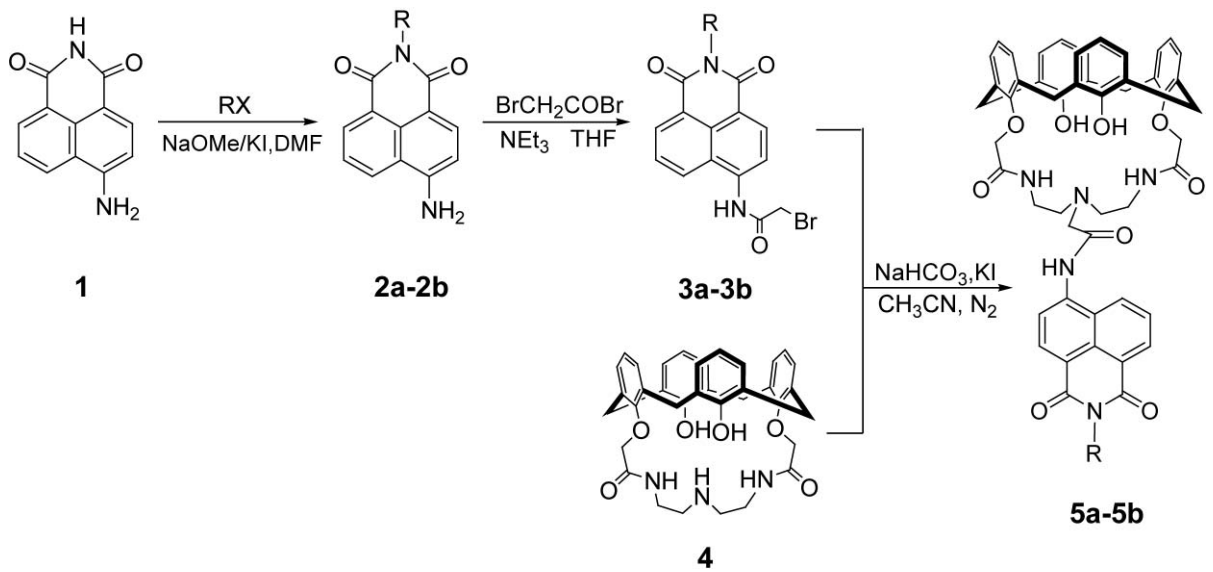
Experimental

Melting points were measured on a Yanagimoto MP-500 apparatus (uncorr).The FT-IR spectra (KBr pellets) were measured on a BIO-RAD FTS3000 IR spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO using TMS as an internal standard on a Varian Inova 500 MHz and 75 MHz at 298K. Mass spectra were carried out on a LCQ Advantage MAX spectrometer. All reagents are commercially available and purified by standard methods prior to use.

Synthesis of **2a–b***; typical procedure*

To a stirred mixture of 4-aminonaphthalimide **1** (0.42 g, 2 mmol), NaOMe (0.16 g, 3 mmol) and a catalytic amount of KI in DMF (25 mL) was added a bromoalkane (6.66 mmol). The reaction mixture was stirred at 100 °C for 4 h and poured into ice/H_2O (130 mL) to afford a solid which was purified by column chromatography. After purification, all the products were characterised by their spectra.

N-Ethyl-1, 8-naphthalimide(**2a**): Orange solid, yield 51%, m.p. 275–279 °C; IR (KBr, cm^{-1}): 3415, 1689; ^{1}H NMR (DMSO-d_6): 8.58



Scheme 1

* Correspondent. E-mail: yqfeng@tju.edu.cn

(d, 1H, *J* = 8 Hz, ArH), 8.40 (d, 1H, *J* = 8 Hz, ArH), 8.16 (d, 1H, *J* = 8 Hz, ArH), 7.64 (t, 1H, *J* = 8 Hz, ArH), 6.80 (d, 1H, *J* = 8 Hz, ArH), 3.98 (t, 2H, *J* = 7.5 Hz, NC**H**$_2$), 3.40 (s, 2H, N**H**$_2$), 1.27 (t, 3H, *J* = 7 Hz, CH$_3$). ^{13}C NMR (DMSO-d6): δ 14.22 (1**C**H$_3$), 33.08 (1N**C**H$_2$), [106.95 (1**C**), 107.84(1**C**), 118.82(1**C**), 121.22 (1**C**), 123.45 (1**C**), 128.88 (1**C**), 129.07 (1**C**), 130.29 (1**C**), 133.43 (1**C**) 152.17 (1**C**)] (Aromatic 10**C**), 162.37 (Hetero 1**C**), 163.28 (Hetero 1**C**). ESI-MS *m/z* 241.3 (M+H)$^+$ (Calcd for $C_{14}H_{12}N_2O_2$ 240.1). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.32; H, 4.98; N, 11.61%.

N-Octyl-1, 8-naphthalimide(**2b**): Orange solid, yield 62%, m.p. 250–255 °C; IR (KBr, cm^{-1}): 3358, 1705; ^{1}H NMR (DMSO-d$_6$): 8.59 (d, 1H, *J* = 8 Hz, ArH), 8.40 (d, 1H, *J* = 8 Hz, ArH), 8.17 (d, 1H, *J* = 8 Hz, ArH), 7.63 (t, 1H, *J* = 8 Hz, ArH), 7.43 (s, 1H, NH$_2$), 6.81 (d, 1H, *J* = 8 Hz, ArH), 3.97 (t, 2H, *J* = 7.5 Hz, NC**H**$_2$), 3.33 (s, 2H, N**H**$_2$), 1.56–1.45 (m, 2H, NCH$_2$C**H**$_2$), 1.28–1.20 (m, 10H, 5CH$_2$), 0.82 (t, 3H, *J* = 7 Hz, CH$_3$). ^{13}C NMR (DMSO-d6): δ 14.31 (1**C**H$_3$), 22.85 (1**C**H$_2$), 27.11 (1**C**H$_2$), 28.92 (1**C**H$_2$), 29.39 (1**C**H$_2$), 29.40 (1**C**H$_2$), 32.01 (1**C**H$_2$), 38.28 (1N**C**H$_2$), [107.03 (1**C**), 107.64 (1**C**), 118.85 (1**C**), 121.28 (1**C**), 123.48 (1**C**), 128.78 (1**C**), 129.17 (1**C**), 130.49 (1**C**), 133.45 (1**C**) 152.19 (1**C**)] (Aromatic 10**C**), 162.39 (Hetero 1**C**), 163.26 (Hetero 1**C**). ESI-MS *m/z* 325.3 (M+H)$^+$ (Calcd for $C_{20}H_{24}N_2O_2$ 324.4). Anal. Calcd for $C_{20}H_{24}N_2O_2$: C, 74.04; H, 7.46; N, 8.64. Found: C, 74.11; H, 7.41; N, 8.61%.

Synthesis of **3a–b***; typical procedure*

To a stirred mixture of *N*-alkyl-1, 8-naphthalimide **2a–b** (0.1 mmol) and NEt$_3$ (0.5 mmol) in dry THF (30 mL) was added a solution of bromoacetyl bromide (2 mmol) in dry THF (20 mL) during 1 h. After the reaction mixture was stirred at reflux temperature for 8 h and then THF was removed in *vacuo*. To the resulting orange solid, water (30 mL) and ethyl acetate (30 mL) were added and the organic phase was separated and washed twice with saturated NaHCO$_3$ and brine, dried over MgSO$_4$ and distilled off to afford a solid which was purified by column chromatography. After purification, all the products were characterised by their spectra.

4-Bromoacetamido-N-ethyl-1, 8-naphthalimide (**3a**): Orange solid, yield 74%, m.p. 221–224 °C; IR (KBr, cm^{-1}): 3415, 1679; ^{1}H NMR (CDCl$_3$): 9.07(s, 1H, CONH), 8.66 (d, 1H, *J* = 8 Hz, ArH), 8.60 (d, 1H, *J* = 8 Hz, ArH), 8.42 (d, 1H, *J* = 8 Hz, ArH), 8.23 (d, 1H, *J* = 8 Hz, ArH), 7.85 (t, 1H, *J* = 8 Hz, ArH), 6.81 (d, 1H, *J* = 8 Hz, ArH), 4.19 (s, 2H, BrCH$_2$CO), 4.11 (t, 2H, *J* = 7 Hz, NC**H**$_2$), 1.29 (t, 3H, *J* = 7 Hz, CH$_3$). ^{13}C NMR (DMSO-d6): δ 14.25 (1**C**H$_3$), 33.08 (1N**C**H$_2$), 36.59 (1Br**C**H$_2$), [106.93 (1**C**), 107.87 (1**C**), 118.82 (1**C**), 121.25 (1**C**), 123.45 (1**C**), 128.90 (1**C**), 129.05 (1**C**), 130.30 (1**C**), 133.43 (1**C**) 152.17 (1**C**)] (Aromatic 10**C**), 162.37 (Hetero 1**C**), 163.28 (Hetero 1**C**), 170.25 (1NCH$_2$**C**O), ESI-MS *m/z* 361.1(M+H)$^+$ (Calcd for $C_{16}H_{13}BrN_2O_3$ 360.0). Anal. Calcd for $C_{16}H_{13}BrN_2O_3$: C, 53.21; H, 3.63; N, 7.76. Found: C, 53.19; H, 3.65; N, 7.72%.

4-Bromoacetamido-N-octyl-1, 8-naphthalimide (**3b**): Orange solid, yield 81%, m.p. 198–202 °C; IR (KBr, cm^{-1}): 3387, 1702; ^{1}H NMR (CDCl$_3$): 9.08 (s, 1H, CONH), 8.64 (d, 1H, *J* = 8 Hz, ArH), 8.60 (d, 1H, *J* = 8 Hz, ArH), 8.43 (d, 1H, *J* = 8 Hz, ArH), 8.21 (d, 1H, *J* = 8 Hz, ArH), 7.83 (t, 1H, *J* = 8 Hz, ArH), 6.81 (d, 1H, *J* = 8 Hz, ArH), 4.20 (s, 2H, BrCH$_2$CO), 4.16 (t, 2H, *J* = 7.5 Hz, NC**H**$_2$), 1.71–1.60 (m, 2H, NCH$_2$C**H**$_2$), 1.29–1.20 (m, 10H, CH$_2$), 0.86 (t, 3H, *J* = 7 Hz, CH$_3$). ^{13}C NMR (DMSO-d6): δ 14.30 (1**C**H$_3$), 22.86 (1**C**H$_2$), 27.12 (1**C**H$_2$), 28.92 (1**C**H$_2$), 29.40 (1**C**H$_2$), 29.41 (1**C**H$_2$), 32.11 (1**C**H$_2$), 36.65 (1Br**C**H$_2$), 38.27 (1N**C**H$_2$), [107.03 (1**C**), 107.64 (1**C**), 118.85 (1**C**), 121.28 (1**C**), 123.48 (1**C**), 128.78 (1**C**), 129.17 (1**C**), 130.49 (1**C**), 133.45 (1**C**) 152.19 (1**C**)] (Aromatic 10**C**), 162.39 (Hetero 1**C**), 163.26 (Hetero 1**C**), 170.80 (1NCH$_2$**C**O). ESI-MS *m/z* 445.4 (M+H)$^+$ (Calcd for $C_{22}H_{25}BrN_2O_3$ 444.3). Anal. Calcd for $C_{22}H_{25}BrN_2O_3$: C, 59.33; H, 5.56; N, 6.29. Found: C, 59.36; H, 5.51; N, 6.27%.

Synthesis of **5a–b***; typical procedure*

Under nitrogen, calix[4]azacrown (**4**)[12] (0.3 g, 0.5 mmol), NaHCO$_3$ (0.2 g, 2.4 mmol), the appropriate 4-bromoacetamido-*N*-alkyl-1, 8-naphthalimide derivatives **3a–b** (1 mmol), and catalytic amount of potassium iodide in acetontrile (30 mL) were heated to reflux temperature. After reflux for 20 hours, acetontrile was removed in *vacuo*. To the resulting yellow solid, water (30 mL) and CH$_2$Cl$_2$ (20 mL) were added and the organic phase was separated and washed twice with distilled water (20 mL). The CH$_2$Cl$_2$ layer was dried over MgSO$_4$ and distilled off to afford a yellowish solid. Column chromatography on silica gel using CH$_2$Cl$_2$/CH$_3$CO$_2$Et = 4/1 as an eluent gave the products. All the products were characterised by their spectra.

N-(N-Ethyl-1, 8-naphthalimide-4-yl)aminocarbonylmethoxy]-calix [4]arene(**5a**): Orange solid, yield 41%, m.p. (>250 °C decomposed); IR(KBr, cm^{-1}): 3302 (–NH), 1664 (C=O), ^{1}H NMR (CDCl$_3$): 9.95 (s, 1H, CONH), 9.11 (t, 2H, *J* = 5.5 Hz, CONH), 8.62(s, 1H, ArH), 8.45 (d, 1H, *J* = 8 Hz, ArH), 8.60–8.56 (m, 2H, ArH), 7.97 (s, 2H, OH), 7.68 (d, 1H, *J* = 8 Hz, ArH), 7.11 (d, 4H, *J* = 7.5 Hz, ArH$_{meta}$), 6.97 (d, 4H, *J* = 7.5 Hz, ArH$_{meta}$), 6.86 (t, 2H, *J* = 7.5 Hz, ArH$_p$), 6.80 (t, 2H, *J* = 7.5 Hz, ArH$_p$), 4.58 (s, 4H, OCH$_2$CO), 4.13 (d, 4H, *J* = 13.5 Hz, ArCH$_2$Ar), 4.15 (t, 2H, *J* = 7 Hz, NCH$_2$), 3.71 (t, 4H, *J* = 5 Hz, CONHCH$_2$CH$_2$), 3.57(s, 2H, NCH$_2$CO), 3.48 (d, 4H, *J* = 13.5 Hz, ArCH$_2$Ar), 3.01–2.90 (m, 4H, NCH$_2$CH$_2$N), 1.22(t, 3H, *J* = 7 Hz, CH$_3$); ^{13}C NMR (CDCl$_3$,): δ 14.44 (1**C**H$_3$), 31.40 (4Ar**C**H$_2$Ar), 40.49 (1N**C**H$_2$), 41.23 (2CONH**C**H$_2$), 55.03 (2N**C**H$_2$), 60.58 (1N**C**H$_2$CO), 75.06 (2**C**H$_2$O), [115.81 (1**C**), 119.01 (2**C**), 120.03 (1**C**), 121.09 (1**C**), 124.64 (1**C**), 126.33 (2**C**), 127.14 (1**C**), 127.78 (1**C**), 127.88 (4**C**), 129.36 (4**C**), 129.57 (1**C**), 130.09 (4**C**), 131.31 (1**C**), 132.85 (4**C**), 132.74 (1**C**), 139.96 (1**C**), 151.23 (2**C**), 152.37 (2**C**)] (Aromatic 34**C**), 164.08 (Hetero 2**C**), 166.60 (2**C**OCH$_2$), 171.42 (1NCH$_2$**C**O). MS *m/z* 888.4 (M+H)$^+$ (Calcd for $C_{52}H_{49}N_5O_9$ 887.4). Anal. Calcd for $C_{52}H_{49}N_5O_9$: C, 70.34; H, 5.56; N, 7.89. Found: C, 70.32; H, 5.61; N, 7.87%.

N-(N-Octyl-1, 8-naphthalimide-4-yl)aminocarbonylmethoxy]-calix [4]arene(**5b**): Orange solid, yield 25%, m.p. (>250 °C decomposed); IR(KBr, cm^{-1}): 3297(–NH), 1671(C=O), ^{1}H NMR(CDCl$_3$): 9.93 (s, 1H, CONH), 9.10 (t, 2H, *J* = 5.5 Hz, CONH), 8.62 (s, 1H, *J* = 8 Hz, ArH), 8.44 (d, 1H, *J* = 8 Hz, ArH), 8.59–8.56 (m, 2H, ArH), 7.95 (s, 2H, OH), 7.68 (d, 1H, *J* = 8 Hz, ArH), 7.12 (d, 4H, *J* = 7.5 Hz, ArH$_{meta}$), 6.96 (d, 4H, *J* = 7.5 Hz, ArH$_{meta}$), 6.85 (t, 2H, *J* = 7.5 Hz, ArH$_p$), 6.79 (t, 2H, *J* = 7.5 Hz, ArH$_p$), 4.58 (s, 4H, OCH$_2$CO), 4.16 (t, 2H, *J* = 7 Hz, NCH$_2$), 4.12 (d, 4H, *J* = 13.5 Hz, ArCH$_2$Ar), 3.70 (t, 4H, *J* = 5 Hz, CONHCH$_2$CH$_2$), 3.59 (s, 2H, NCH$_2$CO), 3.50 (d, 4H, *J* = 13.5 Hz, ArCH$_2$Ar), 3.09–2.92 (m, 4H, NCH$_2$CH$_2$N), 1.34–1.22 (m, 12H, CH$_2$), 0.87 (t, 3H, *J* = 7 Hz, CH$_3$); ^{13}C NMR (CDCl$_3$): δ 14.38 (1**C**H$_3$), 28.37 (1**C**H$_2$), 29.41(1**C**H$_2$), 29.76(1**C**H$_2$), 29.87(1**C**H$_2$), 30.37 (1**C**H$_2$), 31.68 (4Ar**C**H$_2$Ar), 31.81(1**C**H$_2$), 40.49 (1N**C**H$_2$CH$_2$CH$_2$), 40.70 (2CONH**C**H$_2$), 55.19 (2N**C**H$_2$), 61.27 (1N**C**H$_2$CO), 75.16 (2**C**H$_2$O), [114.31 (1**C**), 118.97 (2**C**), 120.08 (1**C**), 121.40 (1**C**), 124.93 (1**C**), 126.44 (2**C**), 127.18 (1**C**), 127.77 (1**C**), 127.84 (4**C**), 129.33 (4**C**), 129.4 (1**C**), 130.04 (4**C**), 131.27 (1**C**), 132.64 (4**C**), 132.70 (1**C**), 139.68 (1**C**), 150.92 (2**C**), 151.93 (2**C**)] (Aromatic 34**C**), 164.50 (Hetero 2**C**), 169.34 (2**C**OCH$_2$), 170.56 (1NCH$_2$**C**O). MS:*m/z* 970.9 (M-H)$^+$ (Calcd for $C_{58}H_{61}N_5O_9$ 971.9). Anal. Calcd for $C_{58}H_{61}N_5O_9$: C, 71.66; H, 6.32; N, 7.20. Found: C, 71.64; H, 6.33; N, 7.22%.

According to the reported literature by Kim,[13] reaction of calix[4]azacrown **4** with *N*-(1-pyrenylmethyl)chloroacetamide using K$_2$CO$_3$ as a base in acetonitrile with a catalytic amount of sodium iodide provided a bis-o-substituted product in medium yield. However, under similar conditions, *N*-substituted-calix[4](aza)monocrown **5a–5b** were obtained with high regioselectivity

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References

1 P.A. Gale, *Coord. Chem. Rev.*, 2001, **213**, 79.
2 C. Suksai and T. Tuntulani, *Chem. Soc. Rev.*, 2003, **32**, 192.
3 S.Y. Lee, S.H. Kim, S.K. Kim, J.H. Jung and J.S. Kim, *J. Org. Chem.*, 2005, **70**, 9288.
4 J.S. Kim, O.J. Shon, J.A. Rim, S.K. Kim and J. Yoon, *J. Org. Chem.*, 2002, **67**, 2348.
5 P.D. Beer and P.A. Gale, *Angew. Chem. Int. Ed.*, 2001, **40**, 486.
6 A. Hamdi, Y.H. Lee, Y. Kim, D.K.A. Kusumahastuti, K. Ohto, R. Abidi and J. Vicens, *Tetrahedron*, 2009, **50**, 540.
7 T.C. Barros, G.R. Molinari, P.B. Filho, V.G. Toscano and M.J. Politi, *J. Photochem. Photobiol. A.*, 1993, **76**, 55.

8 Z.C. Xu, S.K. Kim, H.N. Kim, S.J. Han, C.M. Lee, J.S. Kim, X.H. Qian and J.Y. Yoon, *Tetrahedron Lett.*, 2007, **48**, 9151.
9 A.L. Koner, J. Schatz, W.M. Nau and U. Pischel, *J. Org. Chem.*, 2007, **72**, 3889.
10 I.A. Bagatin, A.T. Cruz, H.E. Toma, M.J. Politi and G.J.F. Demets, *J. Inclu. Phenom. Macro. Chem.*, 2005, **52**, 189.
11 C. Jaime, J.D. Mendoza, P. Prados, P.M. Nieto and C. Sanchez, *J. Org. Chem.*, 1991, **56**, 3372.
12 K. No, H.J. Lee, K.M. Park, S.S. Lee, K.H. Noh, S.K. Kim, J.Y. Lee and J.S. Kim; *J. Heterocyl Chem.*, 2004, **41**, 211.
13 J.Y. Lee, S.K. Kim, J.H. Jung and J.S. Kim, *J. Org. Chem.*, 2005, **70**, 1463.