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A convenient method for the preparation of mono *N*-alkylated cyclams and cyclens in high yields

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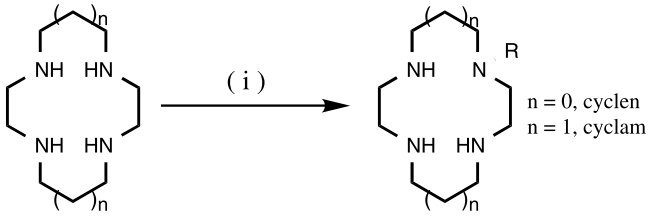
Abstract—Selective and high yield synthesis of mono *N*-substituted derivatives of cyclam and cyclen can be achieved by using a direct and general synthetic method with very mild reaction conditions.

The complexation chemistry of functionalized cyclams and cyclens has been extensively studied in recent years. The main reasons are that these macrocycles have strong coordination ability towards a wide range of cations, including transition metal ions and lanthanide ions, and their complexes demonstrate high thermodynamic stability and kinetic inertness.[1a,b] Hence cyclam and cyclen have become the two most important tetraazamacrocycles in application and research, and their complexes have been widely used as MRI contrast agents,[1b,c] luminescent probes,[2] DNA cleavers[3] and medicines for radioimmunotherapy.[4] Currently, one approach in MRI contrast agents focuses on the feasibility of introducing some special functional groups into the macrocycles, which can improve tissue selectivity, modify biodistribution, and give the molecule the ability to sense pH value, temperature, and even enzymatic activity.[5]

Selective mono *N*-alkylation is an important step in the preparation of functionalized macrocycles. Several routes for mono *N*-alkylation have been reported. Direct *N*-alkylations have been attempted, but a large excess amount of costly polyazacrowns are needed.[6] Three amines in the cyclic tetraamine are temporarily protected by protective groups such as *tert*-butyloxycarbonyl, tosyl and formyl, before the alkylation is performed.[7] Another method is the introduction of some sterically hindered reagents including boron,[8] phosphoryl species,[9] glyoxal aminal,[10] and metal carbonyls $M(CO)_6$ (M = Cr, Mo, W)[11] in a stoichiometric ratio, which can temporarily block three of the nitrogen atoms from the inside of the tetraazamacrocycles. However, all these procedures involve a protection, mono functionalization, and deprotection sequence. Such multiple step routes are divergent and not always applicable; special reagents and extreme reaction conditions are needed in some cases. This prompted us to look for a more convenient and straightforward procedure with high selectivity and high yield.

As a general synthetic method, the tetraazamacrocycles should be able to react with different activated or non-activated alkyl bromides, and bromides containing functional groups that play an important role in enhancing the molecule's special performance. Here, we describe a general and convenient route for obtaining the mono *N*-alkylated derivatives of cyclam and cyclen. Under these reaction conditions, satisfactory selectivity and yield were achieved (Scheme 1).

A typical procedure is as follows: alkylating agent (0.2 mmol) in 10 mL acetonitrile was added dropwise under nitrogen to a solution of the tetraazamacrocycle (cyclam or cyclen, 0.4 mmol) in 40 mL of acetonitrile with 1.0 mmol anhydrous K_2CO_3 at 55–60°C. This process lasted for about half an hour. The mixture was



Scheme 1. Reagents and conditions: (i) 0.4–0.5 equiv. of alkylating reagents, CH_3CN, 55–60°C, K_2CO_3, N_2.

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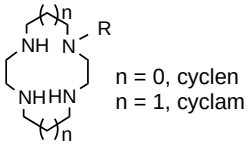
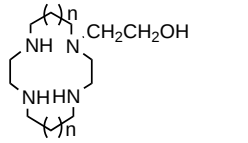
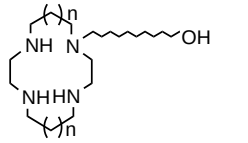
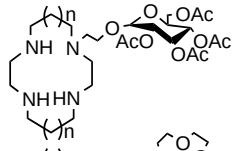
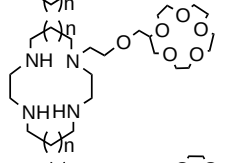
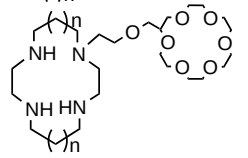
then stirred for another 3–10 h at the same temperature. The reaction was monitored by TLC (Al_2O_3, chloroform/methanol) until all of the alkylating agent was consumed. After cooling down to room temperature, the excess macrocycles and K_2CO_3 were filtered and the solvent was evaporated below 30°C to leave the crude products, which were purified by flash chromatography on aluminum oxide (neutral, 70–230 mesh) with a chloroform/methanol (or ethyl acetate/hexane) mixed solvent system. A small amount of bis-alkylated macrocycles and tri-alkylated macrocycles were observed together with mono *N*-alkylated products. Various selected alkylating reagents and their mono *N*-alkylated products are listed in Table 1.

From Table 1 we find that the macrocycle:alkylating agents ratio of 2–2.5:1 is the best choice for these reactions; increasing the amount of tetraazamacrocycles does not further improve the selectivity and yield. Accordingly, 2 equiv. of tetraazamacrocycles versus alkylating agents is necessary to maintain the high yield of mono *N*-alkylated products. From Table 1, under the same reaction conditions, cyclam shows better mono *N*-alkylation selectivity and yield than cyclen. We found that the solubility of cyclam and cyclen in acetonitrile is different. The limited solubility of cyclam and the high solubility of mono *N*-alkylated cyclam in acetonitrile are presumed to afford the driving force for the reaction.

Previously Kruper and co-workers found that a high yield of mono *N*-alkylated products in the form of monohydrohalide salts can be obtained from the reaction of a stoichiometric amount of cyclen with α-bromo acid esters in a nonpolar, aprotic solvent.[12] Unfortunately, we found that the high yield cannot be maintained in the case of some less active bromides or alkyl bromides with special functional groups. Moreover,

Table 1. Alkylation of cyclam and cyclen with alkyl bromides

Electrophile	Product	Time (h)		% Isolated yield [a] mono-subs	bis-subs	tris-subs	*m/z* (MH^+)[b]
$BrCH_2COOCH_2CH_3$ **1a**	 n = 0, cyclen; n = 1, cyclam; R = $CH_2COOCH_2CH_3$, $PhCH_2$, $CH_2{=}CHCH_2$	4	**1** n = 0	79	~5	~2	259.3
		4	**1** n = 1	85	~3	~1	287.3
2a		4	**2** n = 0	81	~3	~1	263.4
		3.5	**2** n = 1	88	~3	n. d.[c]	291.4
$CH_2{=}CHCH_2Br$ **3a**		4	**3** n = 0	84	~2	~1	213.3
		4	**3** n = 1	91	~2	n. d.[c]	241.4
$Br\ CH_2CH_2OH$ **4a**		6	**4** n = 0	83	~3	n. d.[c]	217.3
		6	**4** n = 1	90	n. d.[c]	n. d.[c]	245.4
Br **5a** OH		6.5	**5** n = 0	83	~2	~1	343.5
		6.5	**5** n = 1	93	n. d.[c]	n. d.[c]	371.4
Br **6a**[13]		8.5	**6** n = 0	75	~4	~1	547.6
		8.5	**6** n = 1	83	~3	~1	575.4
Br **7a**[14]		8.5	**7** n = 0	72	~5	~2	449.5, 471.5[d]
		8.5	**7** n = 1	81	~5	~1	477.5, 499.5[d]
Br **8a**[15]		10	**8** n = 0	66	~5	~3	493.7, 515.6[d]
		10	**8** n = 1	78	~3	~2	521.7, 543.6[d]

[a] All the reactions were conducted at 55–60°C in dry acetonitrile under a N_2 atmosphere; selectivity and yield were based on products isolated by flash column chromatography. The two starting materials were in the ratio of macrocycle:alkylating agents = 2–2.5:1 and 5.0 equiv. of anhydrous potassium carbonate was added to the base. [b] ESI-MS *m/z* [MH^+]. [c] Product was not detected. [d] ESI-MS *m/z* [M+Na]$^+$.

Table 2. Alkylation of cyclam and cyclen in the different solvents

Macrocycle	Alkylating agent	% Isolated yield			
		CH_3CN[a]	$CHCl_3$[b]	$CHCl_3$[a]	EtOH[a]
Cyclen	$PhCH_2Br$	81	84	43	~3
	CH_2=$CHCH_2Br$	84	81	51	~5
	$BrCH_2COOEt$	79	85	47	~3
	$Br(CH_2)_{11}OH$	83	43	32	~6
	$BrCH_2CH_2OCH_2$-15-crown-5	72	38	21	~2
	$BrCH_2CH_2O$-β-D-glucopyranoside	75	32	31	~1
Cyclam	$PhCH_2Br$	88	55	47	~4
	CH_2=$CHCH_2Br$	91	53	55	~6
	$BrCH_2COOEt$	85	49	44	~5
	$Br(CH_2)_{11}OH$	93	28	37	~7
	$BrCH_2CH_2OCH_2$-15-crown-5	81	n.d.[c]	24	~2
	$BrCH_2CH_2O$-β-D-glucopyranoside	83	n.d.[c]	36	~2

[a] Isolated yield of purified product after flash chromatography. All reactions were conducted at 55–60°C; reaction time ranged from 3 to 10 h. All the reactions were conducted at the ratio of macrocycle:alkylating agent = 2–2.5:1, and 5.0 equiv. of anhydrous potassium carbonate was added as base.

[b] Using similar reaction conditions as in Ref. 12.

[c] Product was not detected.

under these reaction conditions, the yields of mono *N*-alkylated cyclams dropped sharply, even for the active *N*-alkylating agents and almost no *N*-alkylated products were observed for the alkylating agents with some large functional groups. In order to clarify the effect of the reaction conditions on the yield of mono *N*-alkylated products of these two important polyazamacrocycles, we conducted experiments using selected *N*-alkylating agents under different conditions. The following observations were made from the data shown in Table 2: (1) In the acetonitrile/K_2CO_3 reaction system, not only high selectivity and yield of mono *N*-alkylated products can be gained for active bromides, but also for less active bromides such as the special alkyl bromides containing β-D-glucopyranoside,[13] long aliphatic chain and different size crown ethers.[14,15] (2) Under these reaction conditions, satisfactory results were achieved for both cyclen and cyclam, and to our surprise, nearly all the *N*-alkylating agents show high activity and selectivity to cyclam, especially in the case of the bromide with a long carbon chain. It is also clear that solvents play an important role in this reaction because poor selectivity and yield resulted in either chloroform or ethanol under the same conditions.

In general, compared with the traditional statistical method, in which a large excess of cyclic tetraamines (5–10 equiv.) versus alkylating agent was used, the amount of cyclic tetraamines required is substantially less in this method. Furthermore, no special reagents, strong acid (base) or extreme temperature are needed in this method, which is very important for introducing pH, temperature or enzymatic sensitive organic and biorganic groups to the macrocycles. Finally, the excess cyclam in solid form can be easily separated from the product solution and recycled.

All mono *N*-alkylated products of cyclam and cyclen were characterized by ^1H NMR, ^{13}C NMR and MS spectra. This straightforward one-step process provides a convenient preparative method for mono *N*-alkylated tetraazamacrocycles such as cyclam and cyclen. The mild and general reaction conditions also allow the possibility of adding macromolecules or biomolecules to tetraazamacrocycles with high efficiency.

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References

1. (a) Alexander, V. *Chem. Rev.* **1995**, *95*, 273–342; (b) Caravan, P.; Ellison, J. J.; McMurry, T. J.; Lauffer, R. B. *Chem. Rev.* **1999**, *99*, 2293–2352; (c) Bianchi, A.; Calabi, L.; Corana, F.; Fontana, S.; Losi, P.; Maiocchi, A.; Paleari, L.; Valtancoli, B. *Coord. Chem. Rev.* **2000**, *204*, 309–393.
2. Reany, O.; Gunnlaugsson, T.; Parker, D. *Chem. Commun.* **2000**, 473–474.
3. Epstein, D. M.; Chappell, L. L.; Khalili, H.; Supkowski, R. M.; Horrocks, W. D., Jr.; Morrow, J. R. *Inorg. Chem.* **2000**, *39*, 2130–2134.
4. (a) Brechbiel, M. W.; Pippin, C. G.; McMurry, T. J.; Milenic, D.; Roselli, M.; Colcher, D.; Gansow, O. A. *J. Chem. Soc., Chem. Commun.* **1991**, 1169–1170; (b) Kumar, K.; Magerstädt, M.; Gansow, O. A. *J. Chem. Soc., Chem. Commun.* **1989**, 145–146.

5. Moats, R. A.; Fraser, S. E.; Meade, T. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 726–728.
6. (a) Studer, M.; Kaden, T. A. *Helv. Chim. Acta* **1986**, *69*, 2081–2086; (b) Chaumei, H.; Handel, H.; Appriou, P.; Guglielmetti, R. *Eur. Polym. J.* **1987**, *23*, 585; (c) Helps, I. M.; Parker, D.; Morphy, J. R.; Chapman, J. *Tetrahedron* **1989**, *45*, 219–226.
7. (a) Kimura, E.; Aoki, S.; Koike, T.; Shiro, M. *J. Am. Chem. Soc.* **1997**, *119*, 3068–3076; (b) Dischino, D. D.; Delaney, E. J.; Emswiler, J. E.; Gaughan, G. T.; Prasad, J. S.; Srivastava, S. K.; Tweedle, M. F. *Inorg. Chem.* **1991**, *30*, 1265–1269; (c) Boldrini, V.; Giovenzana, G. B.; Pagliarin, R.; Palmisano, G.; Sisti, M. *Tetrahedron Lett.* **2000**, *41*, 6527–6530.
8. Bernard, H.; Yaouanc, J. J.; Clément, J. C.; des Abbayes, H.; Handel, H. *Tetrahedron Lett.* **1991**, *32*, 639–642.
9. Filali, A.; Yaouanc, J. J.; Handel, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 560–561.
10. Rohovec, J.; Gyepes, R.; Císařová, I.; Rudovský, J.; Lukeš, I. *Tetrahedron Lett.* **2000**, *41*, 1249–1253.
11. (a) Patinec, V.; Yaouanc, J. J.; Clément, J. C.; Handel, H.; des Abbayes, H. *Tetrahedron Lett.* **1995**, *36*, 79–82; (b) Yaouanc, J. J.; Le Bris, N.; Le Gall, G.; Clément, J. C.; Handel, H.; des Abbayes, H. *J. Chem. Soc., Chem. Commun.* **1991**, 206–207.
12. Kruper, W. J., Jr.; Rudolf, P. R.; Langhoff, C. A. *J. Org. Chem.* **1993**, *58*, 3869–3876.
13. *Synthesis of 2,3,4,6-tetraacetyl-1-(2-bromoethoxy)-D-glucopyranoside* (**6a**): 1.5 equivalents of 2-bromoethanol (5.6 g, 45 mmol) was added to the solution of the penta-*O*-acetyl D-glucopyranose (11.7 g, 30 mmol) in dichloromethane (80 mL). Boron trifluoride etherate (28.5 mL, 225 mmol) was added to the stirred solution at 0°C for 1 h and then at 35°C overnight. The solution was washed with water, aqueous sodium carbonate and saturated aqueous sodium chloride, respectively, dried with magnesium sulfate and evaporated in vacuo to give the crude product (12.02 g, 26.4 mmol) as a yellow oil, yield: 88%. Diethyl ether (50 mL) was added and the mixture was placed in a refrigerator overnight during which time a white solid precipitated. The white solid was recrystallized from diethyl ether to yield white needle-like single crystals. mp: 119–120°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.22 (1H, t, $J=10$ Hz, Glc-H3), 5.08 (1H, t, $J=10$ Hz, Glc-H4), 5.02 (1H, t, $J=10$ Hz, Glc-H2), 4.57 (1H, d, $J=8$ Hz, Glc-H1), 4.26 (1H, dd, $J=12$, 5 Hz, Glc-H5), 4.20–4.12 (2H, m, Glc-H6a, b), 3.86–3.80 (1H, m, α-a), 3.78–3.68 (1H, m, α-b), 3.46 (2 H, t, $J=6$ Hz, β-a, b), 2.09 (3H, s, Ac), 2.07 (3H, s, Ac), 2.03 (3H, s, Ac), 2.01 (3H, s, Ac); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 170.1, 169.3, 100.9, 72.5, 71.8, 70.9, 69.7, 68.2, 61.7, 29.8, 20.6, 20.5. FAB-MS: m/z 455 $[M]^+$, 477 $[M+Na]^+$. Anal. Calcd for $C_{16}H_{23}O_{10}Br$: C, 42.21; H, 5.09. Found: C, 42.36; H, 5.34%.
14. *Synthesis of 2-(2-bromoethoxy)methyl-15-crown-5* (**7a**): 300 mg (1.2 mmol) hydromethyl-15-crown-5 and 75 mg (0.4 mmol) triethylbenzyl ammonium chloride were added to dibromoethane (10 mL) at the same time. An aqueous solution of 50% sodium hydroxide (5 mL) was added and stirred at 60°C for about 12 h. After cooling, dichloromethane (10 mL) and H_2O (10 mL) were added and collected separately after extraction. The aqueous phase was further extracted with dichloromethane (3×10 mL), the combined organic fractions were evaporated to give the crude product as a yellow oil, which was purified by column chromatography on aluminum oxide (neutral, 70–230 mesh) with ethyl acetate:hexane = 7:3 as eluent. Yield: 67% as a pale viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86–3.54 (23H, m, 11×O-CH_2 and 1×O-CH), 3.44 (2H, t, $J=6$ Hz, CH_2-CH_2-Br); ^{13}C NMR (100 MHz, $CDCl_3$): δ 78.7, 71.5, 71.4, 71.2, 71.1, 70.9, 70.8, 70.7, 70.6, 70.5. 70.4, 70.3, 30.5. ESI-MS: m/z 357.5 $[M]H]^+$, 379.5 $[M+Na]^+$. Anal. Calcd for $C_{13}H_{25}O_6Br$: C, 43.71; H, 7.05. Found: C, 43.56; H, 7.35%.
15. *Synthesis of 2-(2-bromoethoxy)methyl-18-crown-6* (**8a**): the synthesis of 2-(2-bromoethoxy)-methyl-18-crown 6 is similar to that of **7a**. Yield: 65% as a pale viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81–3.54 (27H, m, 13×O-CH_2 and 1×O-CH), 3.45 (2H, t, $J=6$ Hz, CH_2-CH_2-Br); ^{13}C NMR (100 MHz, $CDCl_3$): δ 78.7, 71.5, 71.4, 71.3, 71.2, 71.1, 71.0, 70.9, 70.8, 70.7, 70.6, 70.5. 70.4, 70.3, 30.5. ESI-MS: m/z 401.4 $[M]H]^+$, 423.4 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{29}O_7Br$: C, 44.90; H, 7.28. Found: C, 44.66; H, 7.57%.