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Mono N-Alkylation and N-Acylation of Cyclen and Cyclam *via* Their Metaltricarbonyl Complexes (M = Cr, Mo)

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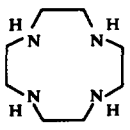
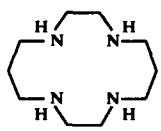
Abstract *: Reaction of metaltricarbonyl complexes of cyclen and cyclam with enolisable aldehydes or acid chlorides yields, after removal of the protecting $M(CO)_3$ moiety, selectively mono N-functionalized derivatives.*

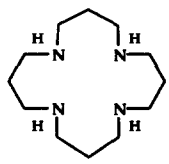
Synthesis and studies of tetraazamacrocycles with pendent arms or *Lariats*[1] have attracted considerable attention owing to their complexing properties[2] - in particular towards lanthanides and heavy metal cations - which have allowed to find medicinal applications[2,3] to derivatives of cyclen (1,4,7,10-tetraazacyclododecane) (**1a**).



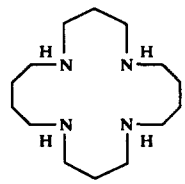
1a



2a



3a



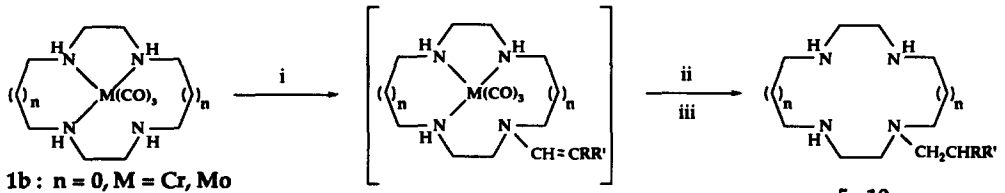
4a

These applications generally require selective N-alkylation of these cyclic tetraamines. A few routes for mono N-alkylation have already been described : the first ones, consisting in introducing the alkyl group prior to the cyclisation step is time-consuming and thus limited in the choice of the group[4] ; then, statistic methods, using either an expensive excess of cyclic tetraamine *versus* alkylating agent[5] or, more recently, a stœchiometric quantity[6] of a sterically hindered reagent, have been designed, but necessitate purification steps to obtain the pure mono N-alkylated tetraamine. A different way consists in temporarily protecting three amine functions of the cyclic tetraamine, involving a protection/mono N-alkylation/deprotection sequence from boron or phosphorus species[7].

In previous papers, group 6 carbonyl metals $M(CO)_6$ (M = Cr, Mo, W) have shown their ability to coordinate three nitrogen atoms of linear or cyclic tetraamines[8,9] to give metaltricarbonyl complexes $LM(CO)_3$ which have already allowed their selective mono- or dialkylation (L = linear tetraamine)[10].

A first result of mono N-alkylation of cyclen (**1a**) and cyclam (1,4,8,11-tetraazacyclotetradecane) (**2a**) through the reaction of cyclic tetraamines complexes $LM(CO)_3$ with activated alkyl bromides has been published[9]. Unfortunately, extension to simple alkyl bromides (1equivalent RBr, base, DMF, 100°C) was unsuccessful, $LM(CO)_3$ complex being insufficiently reactive : sodium carbonate (Na_2CO_3, xH_2O) hydrolysed the alkyl bromide (RBr) into the corresponding alcohol (ROH) ; the replacement of Na_2CO_3 by Et_3N did not bring any improvement since use of triethylamine (Et_3N) led to the quaternary ammonium salt ($REt_3N^+Br^-$). Moreover, in the case of cyclen (**1a**), replacement of bromides by iodides led to an unexpected selective N^1,N^7-dialkylation[11]. This prompted us to look for a more general way, and we describe here two new routes for obtaining mono N-functionalized derivatives of cyclen and cyclam with various groups, including lipophilic chains.

The first one is based on the "one-pot" reaction of $LM(CO)_3$ complexes (**1b** and **2b**) with enolisable aldehydes (Scheme 1) in dimethylformamide (DMF) within 4h at 100°C. After reduction *in situ* of the enamine intermediate with sodium borohydride and deprotection by oxidation in 10% HCl with air, mono N-alkylated derivatives were obtained and characterized[12] by conventional techniques (products **5 - 10**, Table 1). It clearly appeared that molybdenum complexes are more reactive than chromium analogues in identical reaction conditions.



1b : n = 0, M = Cr, Mo
2b : n = 1, M = Cr, Mo

5 - 10

Scheme 1 : *Reagents and conditions* : i, 1 eq RR'CHCHO, DMF,100°C ; ii, $NaBH_4$, RT ; iii, O_2, H_3O^+

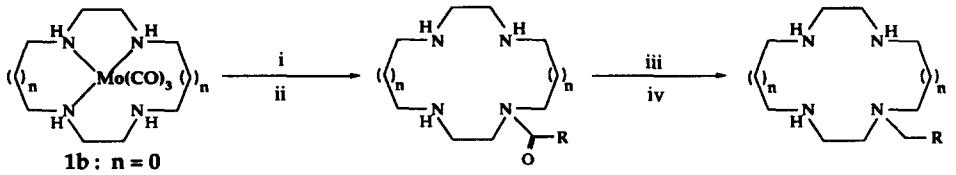
Complexe	R	R'	Yield		Product	m/z (M^+)
			M = Cr	M = Mo		
1b	H	Ph	52	86	**5**	304 (<1%)
	Ph	Ph	-	35	**6**	352 (1%)
	Ph	CH_3	41	55	**7**	303 (1%)[a]
	H	$CH_3(CH_2)_6$	-	48	**8**	311 (1%)[b]
2b	H	Ph	47	62	**9**	276 (1%)
	H	$CH_3(CH_2)_6$	-	51	**10**	341 (1%)[c]

Table 1 : Mono N-alkylation with enolisable aldehydes.[a] (M-15), [b] (M-1), [c] (M+1).

The second way has been developed by reacting acid chlorides in DMF at room temperature (as shown in Scheme 2), and checked with molybdenum complexes. This first step[13] led to the mono N-acylated tetraamines with good yields (products **11-17**, Table 2).

After reduction of the amide into amine with borane-methylsulfide complex in THF at reflux, mono N-alkylated derivatives were isolated and characterized[14] (products **18 - 24**, Table 2).

In these two methods, separation of mono N-alkylated or N-acylated ligand from unreacted tetraamine was easy since the latter was not extracted at pH 12.



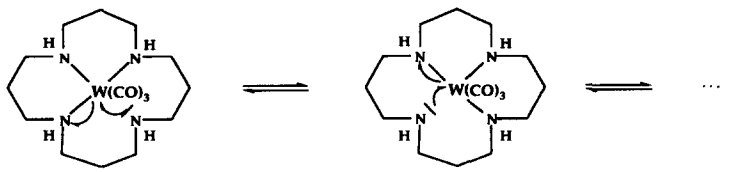
1b : n = 0
2b : n = 1 **11 - 17** **18 - 24**

Scheme 2 : *Reagents and conditions* : i , 1.1 eq RCOCl, 1.1 eq Et_3N, DMF, RT ; ii O_2, H_3O^+ ; iii, 5/3 eq $BH_3.SMe_2$, THF reflux ; iv, H_3O^+ reflux

Complex	R	N-acylation			Reduction		
(M = Mo)		Product	Yield	m/z (M^+)	Product	Yield	m/z (M^+)
1b	Ph	**11**	75	276 (3%)	**18**	75	262 (3%)
	CH_3CH_2	**12**	85	228 (1%)	**19**	74	256 (1%)
2b	Ph	**13**	90	304 (4%)	**20**	73	290 (1%)
	CH_3CH_2	**14**	81	256 (1%)	**21**	57	242 (<1%)
	$CH_3(CH_2)_{10}$	**15**	50	382 (1%)	**22**	50	(a)
	$(CH_3)_2CH$	**16**	76	284 (1%)	**23**	67	(a)
	2-furyl	**17**	65	294 (1%)	**24**	70	(a)

Table 2 : Reaction with acid chlorides. (a) not detected

Complexation of the tetraamines (**3a**) (1,5,9,13-tetraazacyclohexadecane) and (**4a**) (1,5,10,14-tetraazacyclooctadecane) did not lead to the expected *fac*-$LM(CO)_3$ complex, except in one case, when **3a** is reacted with $W(CO)_6$[15]. In the others cases, *cis*-$LM(CO)_4$ or mixtures of *cis*-$LM(CO)_4$/*fac*-$LM(CO)_3$ (that are obviously unsuited for mono alkylation) were obtained.
Reactivity of the [(**3a**)$W(CO)_3$] complex was disappointing since reactions with alkyl halides, enolisable aldehydes and acid chlorides gave mixtures of polysubstituted derivatives. These results suggest the existence of an exchange of coordinated nitrogen atoms which could explain the observed polyalkylation (Scheme 3).



Scheme 3

Despite this discrepancy between the reactivities of tetraazamacrocycle complexes, the two methods described herein represent an interesting stœchiometric alternative to the mono N-alkylation of cyclen and cyclam by non activated alkyl halides.

All the mono N-functionalized tetraamines gave satisfactory ^1H and ^{13}C NMR and mass spectral data.

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12) *Reaction of aldehydes (typical procedure)* : to the complex $LM(CO)_3$[9] (1 mmole) in dry and degassed DMF (10 mL), an excess of dry $MgSO_4$ and the aldehyde (1 mmole) were added . The mixture was heated with stirring under a nitrogen atmosphere at 100°C for 4h. After cooling at RT, $NaBH_4$ (1 mmole) was added and allowed to react overnight. The solvent was removed in *vacuo* and the residue taken up in degassed 10% aqueous HCl. The resulting acidic mixture (pH 1) was oxidized in air until no more CO evolved, and then washed with CH_2Cl_2 (2 x 25 mL). The pH was raised to 14 with NaOH pellets with cooling. After extraction with CH_2Cl_2 (2 x 25 mL), drying and evaporation, the oily residue was found to be pure. *Characteristic NMR data of products* **(5)** and **(10)** ($CDCl_3$) : **(5)** ^{1}H 2.52 (m, 4H) ; 2.59 (m, 4H) ; 2.75 (m, 12H) ; 7.20 (m, 5H). ^{13}C 33.7 ; 45.1 ; 45.8 ; 45.9 ; 51.3 ; 56.1 ; 125.7 ; 128.1 ; 128.7 ; 140.3. **(10)** ^{1}H 0.90 (t, 3H) ; 1.29 (m, 14H) ; 1.55 (m, 4H) ; 1.67 (m, 2H) ; 2.36-2.71 (m, 21H). ^{13}C 14.4 ; 23.1 ; 26.2 ; 26.8 ; 28.0 ; 28.9 ; 29.8 ; 30.1 ; 30.2 ; 30.3 ; 32.3 ; 48.1 48.2 ; 49.3 ; 49.7 ; 49.8 ; 51.5 ; 53.1 ; 54.2 ; 54.9.
13) *Reaction with acid chlorides (typical procedure)* : to the complex $LM(CO)_3$[9] (1 mmole) in dry and degassed DMF (10 mL), Et_3N (1.1 equivalent) and the acid chloride (1.1 equivalent) were added. The mixture was stirred under nitrogen atmosphere at RT for 24 hours. The solvent was removed in *vacuo*. Oxidation and extraction were similar to precedently. *Characteristic NMR data of products* **(12)** (DMSO-d_6,90°C) and **(17)** (toluene-d_8,90°C) : **(12)** ^{1}H 1.01 (t, 3H) 2.35 (q, 2H) ; 2.56 (m, 4H) ; 2.65 (m, 4H) ; 2.75 (m, 4H) ; 3.42 (m, 4H). ^{13}C 8.9 ; 25.6 ; 45.2 ; 47.1 ; 47.6 ; 48.1 ; 173.7. **(17)** ^{1}H 1.21 (s, 3H) ; 1.47 (qt, 2H) , 1.70 (m, 2H) 2.50 (m, 10H) ; 2.76 ; (t, 2H) ; 3.50 (t, 2H) ; 3.69 (t, 2H) ; 6.08 (dd, 1H) ; 6.95 (m, 2H). ^{13}C 30.0 ; 30.2 ; 46.3 ; 46.8 ; 48.0 ; 48.4 ; 48.5 ; 49.0 ; 49.6 ; 50.6 ; 111.3 ; 115.6 ; 143.3 ; 150.4 ; 160.2.
14) *Reduction of amides (typical procedure)* : the mono N-substituted tetraamine was then dissolved in dry THF (100 mL), a solution of $BH_3.SMe_2$ (5/3 equivalents) added, and the mixture refluxed overnight under a nitrogen atmosphere. After cooling, the excess of $BH_3.SMe_2$ was destroyed by slow addition of MeOH, and the solution evapored to leave a white solid. This was taken up in 10% aqueous HCl (100 mL) and refluxed for 12 hours. After cooling, the pH was raised to 14 with NaOH pellets and the product extracted with CH_2Cl_2 (3 x 25 mL). After drying ($MgSO_4$) and evaporation of solvent, pure mono N-alkylated tetraamine was isolated. *Characteristic NMR data of products* **(19)**, **(22)** and **(24)** ($CDCl_3$) : **(19)** ^{1}H 0.87 (t, 3H) ; 1.46 (m, 2H) ; 2.40 (m, 2H) ; 2.56 (m, 4H) ; 2.65 (m, 8H) ; 2.81 (m, 4H). ^{13}C 11.6 ; 19.9 ; 45.43 ; 45.46 ; 47.0 ; 51.0 ; 56.8. **(22)** ^{1}H 0.87 (t, 3H) ; 1.24 (s, 20H) , 1.45 (m, 2H) ; 1.78 (m, 2H) ; 2.40-2.80 (m, 21H). ^{13}C 14.1 ; 22.6 ; 25.3 ; 25.5 27.5 ; 27.6 ; 29.3 ; 29.59; 29.62 29.65 ; 29.70 ; 31.8 ; 47.2 ; 47.4 ; 48.6 ; 49.4 ; 49.6 ; 50.9 ; 52.5 ; 53.5 ; 53.8. **(24)** ^{1}H 1.73 (m, 2H) ; 1.83 (qt, 2H) ; 2.51 (t, 2H) ; 2.65 (m, 16H) ; 3.71 (s, 2H) ; 6.16 (d, 1H) ; 6.30 (dd, 1H) ; 7.34 (dd, 1H). ^{13}C 25.6 28.4 ; 46.9 ; 47.5 ; 47.6 ; 48.8 ; 49.2 ; 49.3 ; 50.5 ; 52.5 ; 54.2 ; 108.6 ; 109.8 ; 141.6 ; 151.7.
15) V. Patinec, J.J. Yaouanc, J.C. Clément, H. Handel, H. des Abbayes, to be published.

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