Mono N-Functionalization of Cyclic and Linear Tetraamines *via* Their Tridentate Tricarbonylchromium Complexes

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The *fac*-$LCr(CO)_3$ tridentate complexes of 1,4,7,10-tetraazacyclododecane **1**, 1,4,8,11-tetraazacyclotetradecane **2**, 1,4,7,10-tetraazadecane **3** and 1,5,8,12-tetraazadodecane **4** have been selectively alkylated in high yield at the uncomplexed nitrogen atom, giving rise to mono *N*-functionalized tetraamines and bis-macrocyclic compounds.

Functionalized macrocyclic polyamines and particularly tetraazacycloalkanes have found a wide range of applications.[1] Similarly, there is increasing interest in linear polyamines, owing to their involvement in many biological processes.[2] Their development is impeded by a frustrating synthetic problem, however: how can these polyamines by mono-*N*-functionalized selectively? So far the question is ill resolved; the action of an alkylating agent gives mixtures unless a procedure involving the tedious use of *N*-protecting organic groups is adopted.[3] It seemed possible to us that a prior complexation of either cyclic or linear tetraamines by reaction with hexacarbonylchromium would give tridentate complexes, keeping one nitrogen atom free from coordination for a further selective monoalkylation.[4†]

We report here our first investigations of this new methodology on four cyclic (**1,2**) or linear (**3,4**) tetraamines (Scheme 1).‡

The following complexation procedure is typical: the tetraamine ligand L (1 mmol) was refluxed under nitrogen for 2 h with $Cr(CO)_6$ (1 mmol) in n-butyl ether (20 ml) at 142 °C. After cooling, the yellow precipitate (85–90% average yield) was separated off. Pertinent ^{13}C NMR and IR data are gathered in Table 1 for complexes **5–8** of the four ligands **1–4**.

IR data are consistent with a local C_{3v} symmetry for the $Cr(CO)_3$ group of the tridentate complexes **5–7**; for **8** an anomaly appears, which will be considered below. ^{13}C NMR data are also consistent with tridentate complexes for **6–8** (**5** is insoluble) showing as expected only one isomer for **6** and **8**; **7** was shown to exist as two stereoisomers§ **7a** and **7b** (1:4 ratio), which after alkylation gave only one compound (see below).

Further alkylation of complexes **5** and **6** either with benzyl and allyl bromides or with *m*- and *p*-dibromoxylenes (Scheme 1, reaction *a*) fully supports these conclusions. The following run is typical: to the complex **5** or **6** (1.0 mmol) in dry dimethylformamide (DMF) (10 ml) was added under nitrogen an excess of dry Na_2CO_3. The stirred mixture was heated at 100 °C and benzyl bromide (1.0 mmol) was added. After heating at 100 °C under N_2 for 1.5 h, the solvent was removed *in vacuo*. The residue was taken up in degassed 10% aqueous HCl and the resulting acidic (pH 1) mixture was then oxidized in air for 12 h. The pH was raised to 14 with KOH pellets with cooling and after extraction with dichloromethane (2 × 50 ml), drying and evaporation, the oily residue was found to

Table 1 IR and ^{13}C NMR data for the $Cr(CO)_3$ moiety of the $LCr(CO)_3$ complexes of **1–4**

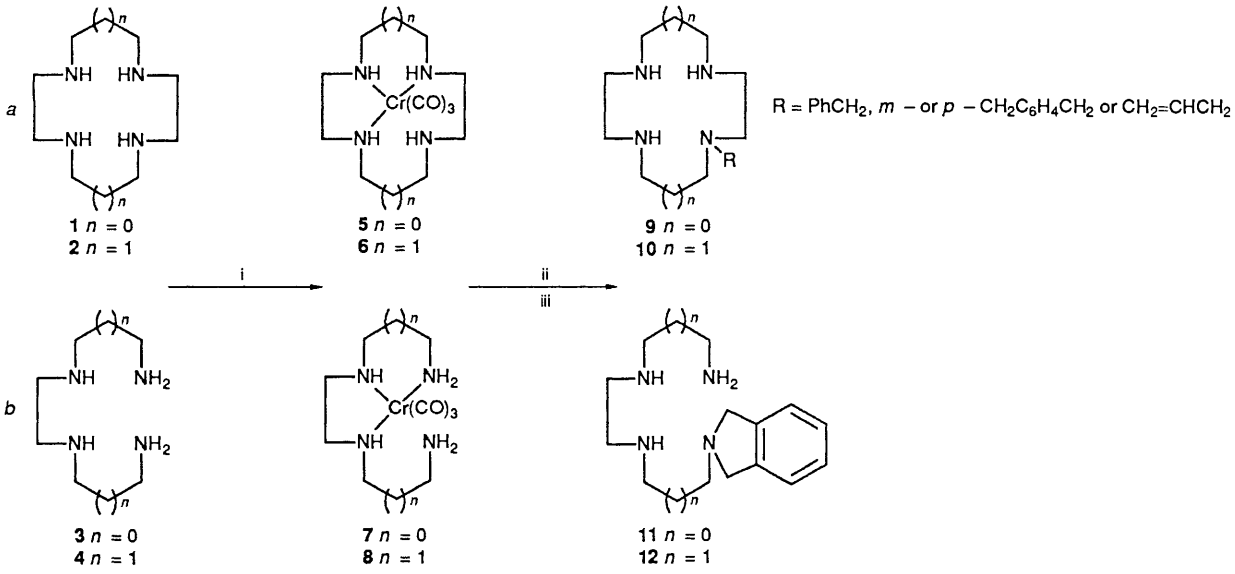
$LCr(CO)_3$	L	IR[a] ν(C≡O)/ cm^{-1}	^{13}C NMR,[b] δ(C≡O)
5	**1**	1895s, 1755vs	Insoluble
6	**2**	1890s, 1750vs	232.8, 232.1, 230.7[c]
7a	**3**	1892s, 1752vs	234.1, 232.5, 230.8[c,d]
7b			233.9, 233.2, 232.4[c,d]
8	**4**	1872, 1740s, 1690s	233.8, 231.6, 230.6[c]

[a] In CH_2Cl_2. [b] 75.47 MHz; CD_3SOCD_3. [c] 1:1:1 intensity. [d] **7a**:**7b**, 1:4.

† The available data concerning complexation modes of polyamines (either cyclic or linear) with metal carbonyls $M(CO)_6$ (M = Cr, Mo, W) are rather limited; *e.g.* diethylenetriamine gives the *fac*-$Cr(CO)_3$ tridentate complex.[4] 1,4,7-triazacyclononane also gives the *fac*-$M(CO)_3$ tridentate complex (M = Cr, Mo).[5] Complexations with $Mo(CO)_6$ of 5,5,7,12,12,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane gives a tridentate *fac*-$Mo(CO)_3$ complex.[6]

‡ Almost the same results (to be published later as a full paper) were obtained with the amines **1–4** following complexation with $Mo(CO)_6$ and $W(CO)_6$ to form tridentate complexes.

§ Detailed NMR studies will be discussed elsewhere.



Scheme 1 *Reagents and conditions*: i, $Cr(CO)_6$; ii, $PhCH_2Br$, $CH_2{=}CHCH_2Br$, p-$BrCH_2C_6H_4CH_2Br$, or m-$BrCH_2C_6H_4CH_2Br$ (reaction *a*); o-$BrCH_2C_6H_4CH_2Br$ (reaction *b*); iii, aerial oxidation, H_3O^+

Table 2 Selected data for mono *N*-alkylated tetramines

	m/z (M^+)	^1H NMR (δ, $CDCl_3$)
9 (R = $PhCH_2$)	262(2%)	7.30 (s, 5H, *Ph*); 3.60 (s, 2H, $PhCH_2$); 2.60 (m, 19H, NCH_2 and NH)
10 (R = $PhCH_2$)	290(1)	7.60 (m, 5H, *Ph*); 3.72 (s, 2H, $PhCH_2$); 2.80 (m, 19H, NCH_2 and *NH*); 1.65–2.0 (m, 4H, NCH_2CH_2–CH_2N)
10 (R = $CH_2{=}CHCH_2$)	240(2)	5.0–6.3 (m, 3H, $CH_2{=}CH$); 3.27 (d, 2H, $CH_2{=}CH$–CH_2); 2.76 (m, 19H NCH_2 + *NH*); 1.40–1.9 (m, 4H, NCH_2CH_2–CH_2N)
9, *meta* (R = CH_2–C_6H_4–CH_2)	446(8)	7.23 (m, 4H, C_6H_4); 3.60 (s, 4H, $CH_2C_6H_4CH_2$); 2.63 (m, 38H, NCH_2 + *NH*)
9, *para* (R = CH_2–C_6H_4–CH_2)		7.13 (m, 4H, C_6H_4); 3.53 (s, 4H, $CH_2C_6H_4CH_2$); 2.62 (m, 38H, NCH_2 + *NH*)
10, *meta* (R = CH_2–C_6H_4–CH_2)	502(3)	7.23 (m, 4H, C_6H_4); 3.56 (s, 4H, $CH_2C_6H_4CH_2$); 2.67 (m, 38H, NCH_2 + *NH*); 1.30–2.0 (m, 8H, NCH_2CH_2–CH_2N)
10, *para* (R = CH_2–C_6H_4–CH_2)	502(5)	7.20 (m, 4H, C_6H_4); 3.48 (s, 4H, $CH_2C_6H_4CH_2$); 2.62 (m, 38H, NCH_2 + *NH*); 1.50–2.0 (m, 8H, $NCH_2CH_2CH_2N$)
11	276(2)	7.06 (s, 4H C_6H_4); 3.80 (s, 4H, o-$CH_2C_6H_4CH_2$); 2.60 (m, 12H, NCH_2); 1.20–2.0 (m, 8H, NCH_2CH_2N + NH)
12		7.04 (s, 4H, C_6H_4); 3.75 (s, 4H, o-$CH_2C_6H_4CH_2$); 2.71 (m, 16H, NCH_2CH_2N + *NH*)

be pure **9** or **10** (R = $PhCH_2$) (respective overall yields 85 and 95%).

A similar reaction scheme (R = $-CH_2C_6H_4CH_2-$) was successfully applied to the synthesis of the bis-macrocycles **9** and **10** (75–90% overall yields (Scheme 1, reaction *a*), and of the mono-*N*-alkylated linear tetramines **11** and **12** (65 and 55% overall yields) (Scheme 1, reaction *b*). This last result established that complexes **7** and **8** were obtained after complexation of three successive nitrogen atoms keeping the terminal primary amino function available for further chemistry.

Furthermore, a careful *in situ* IR observation of the reaction of **8** with *p*-tolualdehyde (CH_2Cl_2, 24 h, room temp., $MgSO_4$ as dessicant) showed the appearance of the normal IR pattern for a *fac*-$LCr(CO)_3$ complex [ν(CO)/cm^{-1} 1890s and 1750vs] in place of the unusual low-frequency CO stretching bands (see Table 1), so it is likely that a strong intramolecular interaction occurs in **8** between the free NH_2 group and the carbonyl ligands of the $Cr(CO)_3$ group, which disappears after reaction with the aldehyde.¶ This interaction cannot occur with complex **7** in which the pendant 'arm' is too short (two methylene groups instead of three).

All the mono *N*-alkylated tetraamines gave satisfactory IR, ^1H and ^{13}C NMR and mass spectral data. Table 2 gives selected data which established the selective mono *N*-alkylation.

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¶ After hydrogenation ($NaBH_4$) of the crude imine, the monofunctionalized tetramine **4** (R = $CH_2C_6H_4Me$) was isolated. ^1H and ^{13}C NMR data were consistent with the proposed formula.