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Study of complexation of mono *N*-alkylcyclen and mono *N*-alkylcyclam with hexacarbonyl metal $M(CO)_6$ (M = Cr, Mo). Specific N^1,N^7-dissymmetric dialkylation of cyclen

Véronique Patinec, Isabelle Gardinier, Jean-Jacques Yaouanc, Jean-Claude Clément, Henri Handel, Hervé des Abbayes *

Laboratoire de Chimie, Electrochimie Moléculaires et Chimie Analytique, URA CNRS No. 322, UFR Sciences et Techniques, Université de Bretagne Occidentale, 6 Avenue Le Gorgeu, BP 809, 29275 Brest Cedex, France

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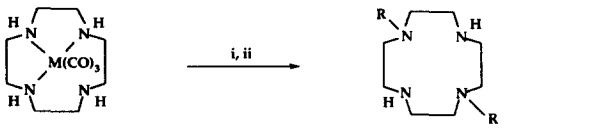
Abstract

Complexation of mono *N*-alkylcyclen (**1**) and mono *N*-alkylcyclam (**2**) with $M(CO)_6$ (M = Cr, Mo) yields only one $LM(CO)_3$ complex, in which the tertiary amine is not coordinated to the metal. An attempted explanation for the N^1,N^7-dialkylation of cyclen, based on an equilibrium between two *fac*-$LM(CO)_3$ (L = mono *N*-alkylcyclen) complexes which are different in the nature of the coordinated nitrogen, is reported. Specific dissymmetric dialkylation of cyclen is also described by a 'one-pot' method and by a 'multi-step' method.

Keywords: Molybdenum complexes; Chromium complexes; Carbonyl complexes; Tetraazamacrocycle complexes; Dialkylation

1. Introduction

Many new macrocyclic compounds have been synthesized in recent years in response to the ever increasing interest in the field of macrocyclic chemistry [1]. Tetraazamacrocycles have been known for a long time now for their ability to form very stable complexes with transition metal cations [2] and, moreover, the chelating properties of these compounds can be adjusted by grafting additional ligating groups on the macrocycle [3]: DOTA (1,4,7,10-tetraazacyclododecane tetraacetic acid) gives thus complexes with alkaline [4] and lanthanide [5] cations, whereas a non-substituted analogue (cyclen: 1,4,7,10-tetraazacyclododecane) presents very little affinity for these same entities. These new properties have enabled the field of applications of these ligands to be enlarged, notably in the medicinal area: the Gd and ^{90}Y complexes of DOTA are at present used respectively in magnetic resonance imaging (MRI) [6] and radioimmunotherapy [7]. If the tetraalkylation of cyclen or cyclam is easily realized, its N^1,N^4 or N^1,N^7 regioselective dialkylation is still a challenge which is at present intensively studied [8]. In this field, we describe here an easy to run synthesis of N^1,N^7 symmetrically and dissymetrically dialkylated cyclen derivatives.



(cyclen)M(CO)$_3$
M=Cr,Mo

Scheme 1. (i) RI, Na_2CO_3, DMF, r.t., 48 h; (ii) O_2, H_3O^+.

Recently we described the stoichiometric mono N-functionalization of cyclen and cyclam (1,4,8,11-tetraazacyclotetradecane) through the reaction of their *fac*-tricarbonyl chromium or molybdenum complexes with various electrophiles including alkyl bromides [9], aldehydes and acid chlorides [10]. Surprisingly, the reaction of cyclen complexes with alkyl iodides yielded regiospecifically the N^1,N^7-disubstituted derivatives [11] after oxidative removal of the $M(CO)_3$ moiety (Scheme 1), instead of the expected mono N-alkylated compound.

In order to obtain further information about the mechanism of this very intriguing reaction, we decided to investigate the mode of recomplexation of mono N-alkylated ligands (**1**, **2**) with hexacarbonyl molybdenum or chromium (Scheme 2) and to compare the reactivity of the resulting complex(es) with that of the mono N-alkylated complex **3** obtained via the classical SN_2 alkylation at the free NH group (Scheme 3).

* Corresponding author.

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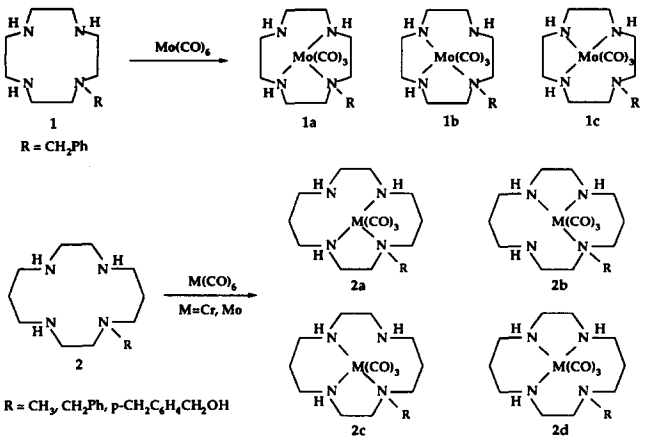
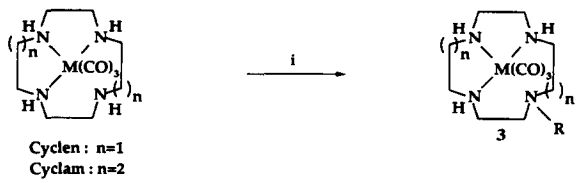


Scheme 2.



Scheme 3. (i) RBr, Na_2CO_3, DMF, 100 °C, 2 h (r.t., 24 h for RX = CH_3I).

2. Experimental

$M(CO)_6$ (M = Cr, Mo) were obtained from Aldrich Chemicals. [(cyclen)$M(CO)_3$] complexes were prepared according to a method described by this laboratory [12]. ^{13}C NMR (75.47 MHz) and ^1H NMR (300 MHz) spectra were measured on a Brucker AC 300 instrument. Mass spectra were realized on a Hewlett Packard GC/MS HP 5995 C instrument. All manipulations were carried out under a nitrogen atmosphere with use of standard Schlenk techniques. Solvents were dried and distilled prior to use.

2.1. Complexes 1c and 2d

Sublimed $M(CO)_6$ (M = Cr, Mo) (1.1 mmol) and cyclic tetraamine (**1** or **2**) (1 mmol) were heated at reflux (142 °C) in di-n-butyl ether (20 ml) for 2 h, while occasionally returning the sublimed $M(CO)_6$ to the reaction solution by scraping the condenser walls. A yellow or beige precipitate formed during the reaction and, after cooling to r.t., the yellow or beige solid was separated off, washed with hexanes (3 × 20 ml) and then dried in vacuo at 50 °C. Yields and characteristic spectral data are gathered in Table 1.

2.2. N^1-Benzyl,N^7-methyl-1,4,7,10-tetraazacyclododecane (4)

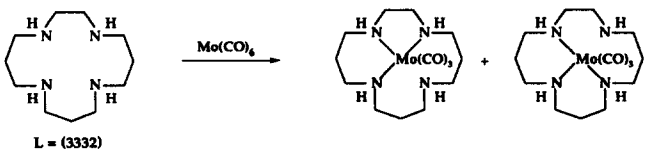
The [(cyclen)$Mo(CO)_3$] [12] complex (1 mmol) was dissolved in dry and degassed *N,N*-dimethylformamide (20 ml); dry Na_2CO_3 (5 mmol) and benzyl bromide (1 mmol) were added and allowed to react with stirring at 120 °C under a nitrogen atmosphere for 2 h. After cooling to r.t., 1 equiv. of methyl iodide (1 mmol) was added and the mixture was allowed to react with stirring for 24 h. A second equivalent of methyl iodide (1 mmol) was then added and allowed to react for 24 h. The solvent was then 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 it was washed with CH_2Cl_2 (2 × 25 ml). The pH was raised to 14 with NaOH pellets with cooling. After extraction with CH_2Cl_2 (2 × 25 ml), drying ($MgSO_4$) and evaporation, the oily residue was found to be pure **4** (yield 0.183 g; 66%).

^1H NMR ($CDCl_3$, ppm): 2.35 (s, 3H, CH_3); 2.50 (s broad, 4H, CH_2 α-N); 2.59–2.64 (m, 12H, CH_2 α-N); 3.61 (s, 2H, $CH_2C_6H_5$); 7.23–7.30 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$, ppm): 43.7 (CH_3); 44.91; 44.93; 51.5; 53.8; 59.5 (CH_2

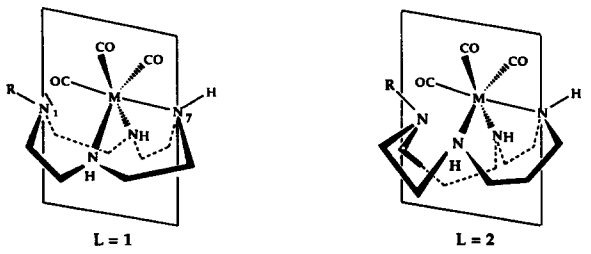
Table 1
Spectroscopic data (IR and ^{13}C NMR) for complexes **1c** and **2d**

Compound	M	R	Yield(%)	IR (cm^{-1})(CH_2Cl_2)	^{13}C NMR (ppm)(DMSO-d_6)
1c	Mo	$-CH_2Ph$	78	1892(s), 1755(vs)	48.2 (CH_2 α-N); 126.9; 128.3; 128.7; 136.2 (C_6H_5); 227.8 (*CO*)
2d	Cr	$-CH_3$	90	1885(s), 1760(vs)	24.6; 25.7 (CH_2 β-N); 43.3; 45.8; 50.5; 51.1; 55.9; 57.6; 59.0 (CH_2 α-N); 231.3; 232.4; 232.7 (*CO*) [a]
	Mo	$-CH_3$	75	1897(s), 1755(vs)	24.3; 24.6 (CH_2 β-N); 43.5; 44.8; 50.3; 51.4; 53.1; 53.6; 55.3; 56.5; 58.6 (CH_2 α-N); 227.4; 228.5; 228.9 (*CO*)
	Mo	$-CH_2Ph$	76	1890(s), 1755(vs)	24.3; 24.4 (CH_2 β-N); 45.0; 49.9; 50.3; 51.2; 53.5; 54.9; 56.3; 56.4; 60.2 (CH_2 α-N); 127.3; 128.2; 128.8; 138.9 (C_6H_5); 227.4; 228.2; 228.5 (*CO*)
	Cr	*p*-$CH_2C_6H_4CH_2OH$	72	1880(s), 1740(vs)	23.97; 24.09 (CH_2 β-N); 44.6; 49.7 (2*C*); 53.2; 53.5; 54.2; 55.4; 56.2; 56.6; 60.5; 62.5 (CH_2 α-N); 126.5; 128.7; 137.7; 141.7 (C_6H_5); 230.7; 232.6 (2*C*) (*CO*)
	Mo	*p*-$CH_2C_6H_4CH_2OH$	75	1898(s), 1762(vs)	24.4 [b] (CH_2 β-N); 45.1; 50.0; 50.3; 53.4; 53.6; 55.2; 56.3; 56.5; 60.0; 62.5 (CH_2 α-N); 126.6; 128.8; 137.1; 141.9 (C_6H_4); 227.6; 228.5; 228.7 (*CO*)

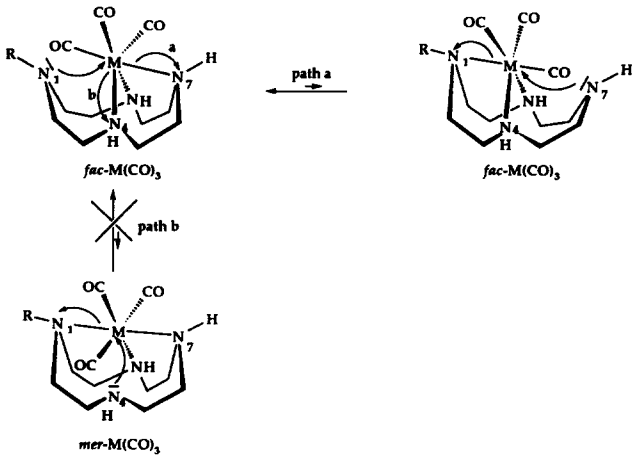
[a] CD_2Cl_2: two peaks masked by the solvent.
[b] Two equivalent peaks for *C* β-N.



Scheme 4.



Scheme 5.



Scheme 6.

α-N); 126.7; 127.9; 128.7; 138.6 (C_6H_5). MS: $m/z=260$ $[M-15]^+$, 3%.

3. Results and discussion

3.1. Complexation of mono N-alkylcyclen (1) and mono N-alkylcyclam (2)

Among the three possible *fac*- or *mer*-$LM(CO)_3$ regioisomers **1a**, **1b** and **1c** (Scheme 2), **1a** and **1b** can be considered respectively as potential precursors for the N^1,N^7- and N^1,N^4-dialkylation of cyclen, and **1c** as a non-reactive species except if the quaternarization of the tertiary amine is wanted.

The recomplexation of a series of mono N-substituted ligands **1** and **2** was run under standard conditions using a slight excess of $M(CO)_6$ in refluxing di-n-butyl ether under N_2 and yielded beige to yellow crystalline powders which precipitated from the reaction medium. After isolation, they were analyzed by ^{13}C NMR (when possible) and IR. Their spectroscopic data were then compared with those of complexes **3** (Scheme 3).

The IR spectra for all the compounds resulting from the recoordination of mono N-alkylated ligands (cyclen or cyclam) are consistent with the presence of a *fac*-$M(CO)_3$ moiety (Table 1) since the two (A_1+E) expected ν(CO) bands for such a structure having a C_{3v} local symmetry are observed.

The ^{13}C NMR spectra of mono N-alkylated cyclenM-$(CO)_3$ derivatives are not informative of any of the possible structures **1a**, **1b** or **1c**: all the signals are coalescing and strongly suggest, on the NMR time scale, the fluxionality of the $M(CO)_3$ tripod which appears as a singlet at about 220–230 ppm.

By contrast, all the (R)cyclam$M(CO)_3$ complexes (see NMR data in Table 1) gave well resolved ^{13}C NMR spectra which exhibit only one set of distinct signals (3 *C*O, 9 *C* α-N and 2 *C* β-N along with the aromatic ones), which means the formation of only one regioisomer **2a**, **2b**, **2c** or **2d**: this reaction of recomplexation is thus regioselective. Actually these spectra are totally superimposable to those of **3** so that **3** and **2d** are the same compound in which the tertiary amine is free. In order to ascertain this, we realized the complexation of a less symmetric macrocycle which was expected to give two regioisomers (Scheme 4): (3332)(1,4,8,12-tetraazacyclopentadecane) actually gave, after reaction with $Mo(CO)_6$, two *fac*-$LM(CO)_3$ compounds [12] easily detected on the ^{13}C NMR spectrum by the two different sets of signals in the ratio (2:1) which means that different regioisomers are distinguishable by NMR.

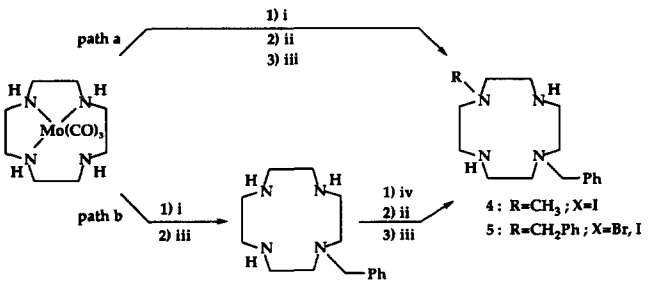
3.2. Discussion

In the difference of fluxionality of the complexes $LM(CO)_3$ (L = **1**, **2**) lies probably the reasons for their different reactivities, particularly in the N^1,N^7-dialkylation of cyclen [11].

Mono *N*-alkylcyclen$M(CO)_3$ (L = **1**), as shown in Scheme 5, possesses a plane of symmetry: the N^1-alkylated nitrogen atom lies exactly in the axis of the metal–N^7 bond allowing, through a '*trans* exchange' mechanism, the existence of an equilibrium (Scheme 6, path a) with a *fac*-$LM(CO)_3$ species, in which the N^7 atom becomes free and reactive enough for a second alkylation. The other possibility (Scheme 6, path b) of an exchange between the N^1 nitrogen atom and the N^4 nitrogen atom is particularly unlikely since it would produce a less stable *mer*-$M(CO)_3$ intermediate, and then, the donor electronic effect of nitrogen would no longer be 'balanced' by the presence in *trans* of a good π-acceptor ligand such as CO.

3.3. N^1,N^7-dialkylation of cyclen

The selectivity of this dialkylation is due to kinetics reasons in the one-pot process. The first SN_2 reaction is very fast and consumes all the electrophile: this is clearly established by the stoichiometric reaction of cyclen with benzylhalides at 100 °C which produces exclusively the mono N-alkylated



Scheme 7. (i) 1 equiv. $PhCH_2Br$, Na_2CO_3, DMF, 110 °C, 1 h 30 min; (ii) 2 equiv. RX, Na_2CO_3, DMF, r.t., 48 h; (iii) O_2, H_3O^+; (iv) 1.1 equiv. $Mo(CO)_6$, Bu_2O, Δ, 2 h.

ligand [9]. Addition of an excess of electrophile at this stage results in a slow second alkylation (24–48 h, r.t.) at the N^7 atom by displacement of the equilibrium, yielding the symmetrically N^1,N^7-dialkylated ligand **5** or the N^1,N^7-dissymetrically derivative **4** if a different electrophile is used (Scheme 7, path a). **4** and **5** can be obtained stepwise by complexation of mono *N*-alkylcyclen with $Mo(CO)_6$ and subsequent reaction with an alkylhalide (Scheme 7, path b).

As the two routes lead to the same result, there is a great probability that the complexation of mono *N*-alkylcyclen (**1**) with $M(CO)_6$ gives complexes of type **1c** in which the tertiary amine is not coordinated to the metal, as established with mono *N*-alkylcyclam derivatives. This specific dialkylation is particular to cyclen complexes since cyclam complexes cannot be dialkylated even under forced conditions — all attempts to dialkylate cyclam complexes failed and yielded only the mono N-alkylated macrocycle. On the contrary, in the case of cyclam complexes which appear to be more rigid as suggested by their well resolved NMR spectra, the N^1 atom is no longer in the metal–N^7 axis because of the presence of a supplementary carbon atom in the propyl bridge which maintains the N^1 atom out of the plane of symmetry, as shown in Scheme 5 (L=**2**). This could explain the difference of reactivity between complexes **1c** and **2d**.

Among the different selective N^1,N^7-difunctionalization processes of cyclen, the only described N^1,N^7-dissymmetric one, which remains without explanation, comes from the neutral hydrolysis of its orthoamide [8b]. Cyclen can easily be ditosylated, diphosphorylated [8c] or dialkoxycarbonylated [8d] when the reaction is run under acidic conditions which favor the protonation, and thus protection, of two very basic [2] opposite nitrogen atoms ($pK_a \sim 10.9$ and 9.8) allowing the two other opposite nitrogen atoms ($pK_a < 2$) to react with an electrophile. The regioselective symmetric or dissymmetric N^1,N^7-dialkylation of cyclen which was achieved under neutral conditions (Na_2CO_3 is used as proton scavenger) with tricarbonyl chromium and molybdenum $LM(CO)_3$ intermediates finds an explanation in an exchange mechanism between two complexes in which the *fac*-$LM(CO)_3$ symmetry is retained.

Acknowledgements

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