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Metal Complexes of a Tetraazacyclotetradecane Bearing Highly Fluorinated Tails: New Catalysts for the Oxidation of Hydrocarbons under Fluorous Biphasic Conditions

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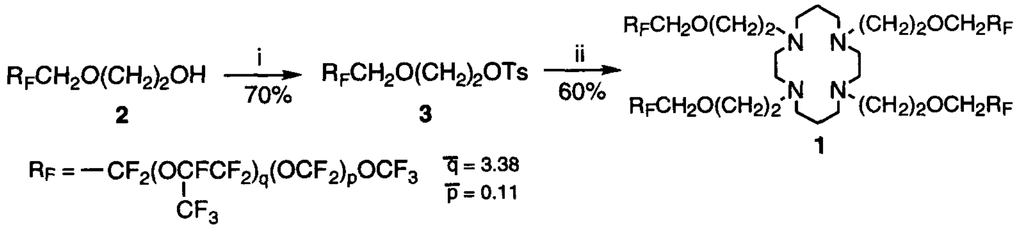
Abstract: The commercially available macrocycle tetraazacyclotetradecane (cyclam) has been converted into the fluorocarbon soluble ligand **1** by N-functionalization with $R_FCH_2OCH_2CH_2OTs$ **3**, wherein R_F is a (per)fluorooxyalkylenic chain. Upon complexation with **1**, transition metal salts can be selectively solubilized in fluorocarbons thus providing new catalysts for the oxidative functionalization of hydrocarbons under fluorous biphasic (FB) conditions. © 1997 Elsevier Science Ltd.

The challenging synthesis of metal complexes selectively soluble in fluorocarbons has so far limited the exploration of the potential of fluorous biphasic (FB) catalysis,[1] a technique based on the low miscibility of fluorocarbons, where the catalyst is confined, with most organic solvents, in which reagents and products are dissolved. The inertness of fluorocarbons and the high oxygen solubility in these fluids would make FB catalysis particularly suited for oxidation reactions.[1c,2] Two of us recently reported the efficient FB epoxidation of alkenes with a combination of molecular oxygen and aliphatic aldehyde, catalyzed by the cobalt complex of a perfluoroalkylated tetraarylporphyrin that was prepared in low overall yield following a multistep pathway.[3]

Seeking a general, simple approach to the synthesis of ligands for FB catalysis, we turned our attention to the functionalization of azamacrocycles. In particular, transition metal complexes of azamacrocycles are able to catalyze the oxidation of hydrocarbons,[4] and can be also prepared *in situ* by addition of inorganic metal salts to the organic solution of the ligand.[4e] The straightforward synthesis of the fluorocarbon soluble tetraazamacrocycle **1** (Scheme 1) is here reported. Copper and cobalt complexes of **1**, easily prepared in perfluorohexane, do act as catalysts for hydrocarbon oxidation under FB conditions. This is the first example of C-H activation mediated by metals under such conditions, leading to alcohols and ketones with a significant turnover number.

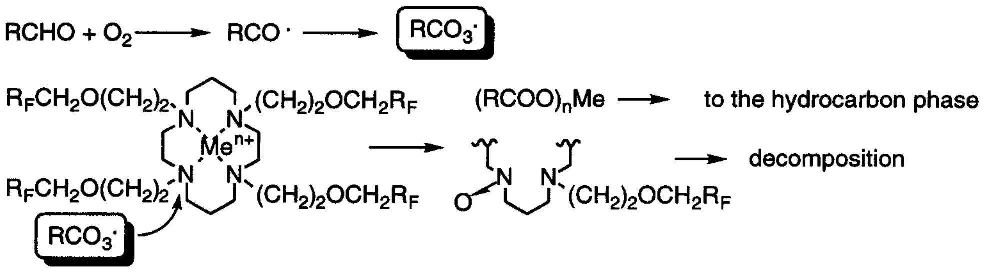


Reagents and conditions: i, *p*-toluenesulphonyl chloride, CH_2Cl_2/50% aqueous NaOH, reflux, 24 h; ii, Cyclam, CH_3CN, Na_2CO_3, reflux, 24 h.

Scheme 1

Commercially available 1,4,8,11-tetraazacyclotetradecane (cyclam) was chosen as starting compound, because of its low cost and easy synthetic manipulation. Moreover cyclam and its N-alkyl derivatives form stable complexes with many transition metal cations.[5] The (per)fluorooxyalkylenic alcohol **2** (Scheme 1), available through an Ausimont proprietory procedure,[6] is an ideal building-block for the functionalization of cyclam. The electron-withdrawing effect of the (per)fluorooxyalkylenic part of the molecule on the N-binding sites of ligand **1** is masked by the interposition of a -$CH_2OCH_2CH_2$- spacer,[1b] that also ensures the absence of elimination reactions during the N-functionalization of cyclam. Alcohol **2** was converted into the corresponding tosylate **3**, then the stoichiometric amount of **3** (4 molar equivalents) was dissolved in CH_3CN and allowed to react with cyclam (1 molar equivalent) at reflux for 24 h in the presence of solid Na_2CO_3. The solvent was evaporated and the residue was extracted with Et_2O, thus affording ligand **1** as a thick oil, freely soluble in cold ether and fluorocarbons, but completely insoluble in cold hydrocarbons.[7]

When an excess of solid CuCl was added to a colourless stirred 1.0 x 10^{-2} M solution of ligand **1** in perfluorohexane, the liquid phase turned immediately green and progressively became darker. The solution was centrifuged and UV-Vis analysis showed the appearance of two broad absorption bands centered at 271 (ε/dm^{-3} mol^{-1} cm^{-1} 754) and 724 nm (ε/dm^{-3} mol^{-1} cm^{-1} 25) respectively. The same procedure was followed with $Ni(ClO_4)_2$ and $Co(ClO_4)_2$, but the liquid phase appeared only slightly coloured after one week and spectroscopic changes were less evident. The extraction of solid metal salts into the fluorocarbon phase containing ligand **1** clearly requires a high binding constant as a driving-force. In fact Cu ions are known to bind much strongly than nichel and Co ions to N-alkylated cyclam derivatives.[8] In order to increase the solubility of metal salts in fluorocarbons, the use of perfluorocarboxylates as counterions was investigated. The Co salt of pentadecafluorooctanoic acid was synthesized according to a procedure originally described by Tuck and coworkers for the preparation of fatty acids salts.[9] Electrochemical oxidation of a Co anode plunged in an acetone solution of the perfluorocarboxylic acid afforded a pink precipitate that was collected and dried in vacuum for 4 h. Elemental analysis was consistent with $(C_7F_{15}COO)_2Co$. This salt was almost insoluble in fluorocarbons, but it was completely solubilized upon addition of one molar equivalent of ligand **1**. The colourless fluorocarbon layer turned blue and two UV absorption bands at 593 (ε/dm^{-3} mol^{-1} cm^{-1} 44) and 640 nm (ε/dm^{-3} mol^{-1} cm^{-1} 47) were observed.[10]



Scheme 2: Pictorial view of the transfer of Cu ions (Me^{n+}) into the hydrocarbon phase in the presence of $RCHO/O_2$.

The catalytic activity of the perfluorohexane solutions of the metal complexes of ligand **1** was tested in the FB oxidation of cyclooctane and cyclohexene. These two model substrates behaved also as the organic phase insoluble in fluorocarbons and were thus used in excess with respect to the oxidant.[11,12] Preliminary experiments showed that the combination O_2/sacrificial aldehyde is not suited for FB oxidations catalyzed by complexes of ligand **1** (Scheme 2). Under the conditions described for homogeneous reactions catalyzed by the Cu complex of 18-crown-6,[12] but using a solution of the Cu complex of **1** in perfluorohexane as catalyst, cyclooctane was converted to cyclooctanone (yield = 77 % based on the starting aldehyde) and cyclooctanol (8.4 %). However, the hydrocarbon layer turned progressively blue as the fluorocarbon layer turned colourless: ligand **1** was destroyed and Cu(II) ions were extracted into the hydrocarbon phase where the oxidation likely occurred (Scheme 2). In the presence of 80% *t*-BuOOH in $(t\text{-BuO})_2$ and molecular oxygen, the two model substrates were converted to mixtures of oxygenated products at room temperature (see Table 1 for results and reaction conditions). UV-Vis spectra of samples of the hydrocarbon phase taken at the end of the reaction did not show absorptions in the 250 - 700 nm range that could be attributed to Cu or Co complexes.

Table 1. Hydrocarbon Oxidation Under FB Condition in the Presence of 80% *t*-BuOOH. [a]

Entry	Substrate	Metal	Time (h)	Substrate Converted [b] (μmol)	Selectivity (%) [c]		Overall Yield [d] (%)	Turnover Number [e]
					Alcohol	Ketone		
1	Cyclooctane	/	24	/	/	/	/	/
2	Cyclooctane	Cu	24	400	20 [f]	80 [g]	80	50
3	Cyclooctane	Co	24	150	24 [f]	76 [g]	30	19
4	Cyclooctane [h]	Cu	24	360	18 [f]	82 [g]	72	40
5	Cyclooctane [i]	Co	24	145	23 [f]	77 [g]	29	18
6	Cyclohexene	/	8	< 50	/	95 [l]	< 10	/
7	Cyclohexene	Cu	8	2570	25 [m]	75 [l]	514	320
8	Cyclohexene	Co	8	2640	18 [m]	82 [l]	528	330
9	Cyclohexene [n]	Cu	8	1240	21 [m]	79 [l]	248	155
10	Cyclohexene [o]	Co	8	2110	21 [m]	79 [l]	422	264

[a] Conditions: Hydrocarbon phase: Substrate (S) = 40 mmol; o-dichlorobenzene (internal standard) = 2 mmol; 80% t-BuOOH (O) = 500 μmol. Fluorocarbon phase: 1 ml of a 8.0×10^{-3} M solution of 1 (C) in perfluorohexane (entries 1 and 6) previously stirred for 1h with an excess of solid CuCl (entries 2 and 7) or $(C_7F_{15}COO)_2Co\cdot$(entries 3 and 8). Molar ratio S/O/C = 5000/62.5/1. Stirring rate = 1300 rpm. T = 20 °C. Reactions were carried out in the dark in the presence of molecular oxygen. Products were identified by comparison with authentic samples and by GC-MS. [b] Determined by GC using the internal standard method. [c] μmol product/μmol converted substrate. [d] Based on the added t-BuOOH. [e] μmol converted substrate/μmol catalyst. [f] Cyclooctanol. [g] Cyclooctanone. [h] Fluorocarbon phase recovered from entry 2; [i] Fluorocarbon phase recovered from entry 3; [l] Cyclohex-2-en-1-one. [m] Cyclohex-2-en-1-ol. [n] Fluorocarbon phase recovered from entry 7. [o] Fluorocarbon phase recovered from entry 8.

Blank reactions (entries 1 and 6) were carried out in the presence of a perfluorohexane solution of free ligand **1**. Only a small amount of cyclohexene was converted to (mainly) cyclohex-2-en-1-one (entry 6), whereas cyclooctane did not react at all (entry 1). When the metal complexes of **1** were used as catalysts, cyclooctane reacted giving a mixture of cyclooctanone and cyclooctanol (molar ratio ~ 4/1, entries 2 and 3). The Cu complex proved to be a better catalyst than the Co one, affording oxygenated products in 80% yield with respect to *t*-BuOOH. Both Cu and Co complexes of **1** catalyze the oxidation of cyclohexene (entry 7 and 8) affording similar results. Only products of allylic attack were detected and the overall amount of alcohol and ketone obtained exceeded about five times the amount of added *t*-BuOOH. The reaction proceeds very likely through an autoxidation mechanism involving cyclohexene hydroperoxide.

Easy recycle of the catalyst is a key-feature of the FB concept.[1] In the present work the fluorocarbon layer recovered at the end of the reaction by simple phase separation was used as such for a second run (entries 4, 5 and 9, 10). The catalytic activity of the fluorocarbon phase was almost completely retained in the oxidation of cyclooctane and in the Co catalyzed oxidation of cyclohexene, whereas 50% of the activity was retained in the case of Cu.

The preliminary results here reported prove that N-functionalization of azamacrocycles with proper perfluoroalkyl tails is a suitable strategy for the synthesis of fluorocarbon soluble ligands. This procedure is much simpler than those required for the synthesis of perfluoroalkyl substituted porphyrins [2c,3] and it opens the way for the realization of other, more efficient fluorous biphasic catalytic systems.

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7. Microanalytical and spectroscopic data for **1**: ^1H NMR ($CDCl_3$) $\delta = 3.80$ (m, 8H), 3.65 (m, 8H), 3.52 (m, 8H), 2.63 (t, $J = 6$ Hz, 8H); 2.49 (s, 8H), 1.59 (q, $J = 6$ Hz, 4H); ^{19}F NMR ($CDCl_3$, ext. ref. $CFCl_3$) $\delta = -50.8$ (s, $-OCF_2O-$), -56.2 (s, CF_3O-), -75.3 (m, $-OCF_2CH_2O-$), -79 - -87 (m, $-O\underline{CF_2}CF(\underline{CF_3})O-$), -144.5 (m, $-OCF_2\underline{CF}(CF_3)O-$); IR (KBr) ν/cm^{-1} 2950, 2884, 2808, 1461, 1235; Anal. Calc. for $C_{71}H_{44}F_{102}N_4O_{22}$: C, 26.30; H, 1.36; N, 1.72; F = 59.76. Found: C, 27.03; H, 1.20; N, 1.91; F = 59.28 %.
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11. Biphasic catalytic oxidation of hydrocarbons is often carried out in the presence of a large excess of substrate, even when a solvent is used. For a recent example see: Battioni, F.; Cardin, E.; Louloudi, M.; Schöllhorn, B.; Spyroulias, G. A.; Mansuy, D.; Traylor, T. G. *Chem. Commun.*, **1996**, 2036-2037.
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