Syntheses and Binding Characteristics of Macrocyclic Systems Containing One to Three β-Diketone Units

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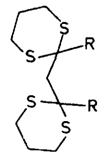
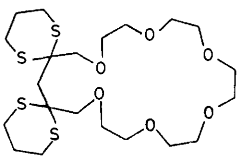
Summary One, two, and three *β*-diketone units have been incorporated into multiheteromacrocycles whose formation constants with metal ions exceed those of an open-chain model by about 1·8 to 6·3 powers of ten.

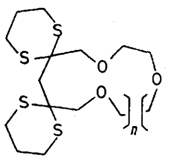
LIGAND assemblies can be structured partially prior to complexation by their incorporation into ring systems, and the resulting ligand organizations in their metal complexes confer special properties on the systems.[1-4] We report here the first incorporation of one, two, and three *β*-diketone units into multiheteromacrocycles and a rough comparison of the complexing properties of the cycles and an open-chain model compound.



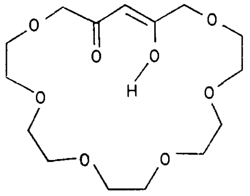
(1) R = H
(2) R = CH$_2$OH



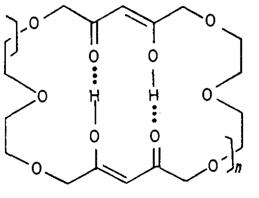
(3)



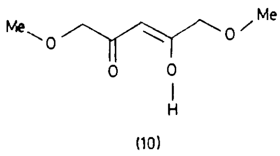
(4) *n* = 1
(5) *n* = 2
(6) *n* = 3



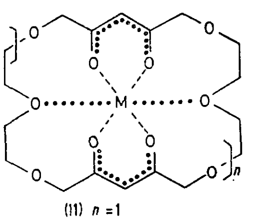
(7)



(8) *n* = 1
(9) *n* = 2



(10)



(11) *n* = 1
(12) *n* = 2

Treatment[2] of (**1**) in tetrahydrofuran (THF) at −30 °C with BuLi (1 equiv.) followed by CH$_2$O (2 equiv.) at −60 °C gave first the monoalcohol which with twice the amounts of the same reagents gave (**2**)† (45%), m.p. 112—114 °C. With pentaethyleneglycol ditosylate, (**2**) and NaH (equimolar) in THF (reflux, 5 h) gave (**3**)†‡ (oil, 90%). With diethyleneglycol ditosylate, (**2**) gave a mixture† (97%) of (**4**) (5%), (**5**) (60%), and (**6**) (30%), whose components were separated‡ and identified by their molecular weights¶ (M.W.), (**4**) giving 384, (**5**) 775, and (**6**) 1140. Methanolysis of (**3**) under N$_2$ in dry degassed THF–MeOH (1:1 v/v) containing HgCl$_2$ (4-fold excess) and CdCO$_3$ (4·5-fold excess) at reflux (4 h) gave ethers which when heated (2 h) in MeCN–10% H$_2$O (v/v), 0·02M in H$_2$SO$_4$, gave (**7**)† (25%).§ Similar treatment of the purified mixture of (**4**), (**5**), and (**6**) gave (**8**) and (**9**)† which were separated to give (**8**)§ (24%, M.W.¶ 905 at 0·050M, 445 at 0·004M) and (**9**)§ (16%, M.W.¶ 1300 at 0·007M, 820 at 0·004M). The open-chain model (**10**)[3] was prepared from (**2**) (32%) through the dimethyl ether of (**2**).†

TABLE. Formation constant data for *β*-diketonides

Ion	Values of log $K_{av.}$ (**8**)	(**9**)	(**10**)	pH range	$\log\left[\frac{K^{f}_{av.}\text{ (cycle)}}{K_{av.}\text{ (model)}}\right]$
Cu^{2+}	11·3	—	9·5	0·5—2·5	1·8
UO$_2$$^{2+}$	11·0	—	8·7	0·5—3·5	2·3
Ni^{2+}	10·8	—	7·0	2—5	3·8
Co^{2+}	9·9	—	6·2	2—5·5	3·7
Zn^{2+}	9·7	—	6·0	2·5—6	3·7
Cd^{2+}	7·9	—	3·9	3—7	4·0
Mn^{2+}	7·6	—	3·3	3—8	4·3
Mg^{2+}	7·4	—	4·5	5—10	2·9
Ca^{2+}	7·8	—	3·1	5—10	4·7
Sr^{2+}	6·7	—	2·7	5—10	4·0
Ba^{2+}	6·4	—	2·5	5—10	3·9
Ce^{3+}	—	11·4	5·1	5—8·5	6·3
La^{3+}	—	10·4	4·5	2·3—9	5·9
Cr^{3+}	—	10·1	5·4	3·5—7	4·7

The pK_a values were determined by titrations with NaOH and HClO$_4$ solutions, 1:1 water–dioxan (v/v) at 24 °C: (**8**) gave pK_as of 8·6 and 11·5; (**9**), 8·6, 11·5, and 13·0; (**10**), 8·6. The formation constants for 14 metal cations (as nitrates) with the cyclic (**8**) and (**9**) and the non-cyclic (**10**) were determined (Table) under N$_2$ in the same medium at 25 °C (K^{f}_{av} at $\bar{n} = 1$ for divalent and $\bar{n} = 3/2$ for trivalent ions in Bjerrum curves).[4] In the calculations of K^{f}_{av}, 1 mol of the bis-*β*-diketone (**8**) was treated as equal

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† Carbon and hydrogen analyses were within 0·30% of theory; ^{1}H n.m.r. spectra in CDCl$_3$ were as expected; 70 eV mass spectra gave the molecular ions.

‡ Purified first by silica gel and then by gel permeation chromatography, 12 ft of BioBeads SX8 in THF, 500 lb in^{-2}.

§ Purified by gel permeation chromatography, 18 ft of Styragel 100 Å in THF, 200—300 lb in^{-2}.

¶ Osmometric molecular weights in CHCl$_3$.

to 2 equiv. and 1 mol of the tris-β-diketone (**9**) as equal to 3 equiv. of 1 mol of (**10**). Equilibration was essentially instantaneous.

A solution of 0·1 mmol of (**8**) in 2 ml of $CHCl_3$ was shaken under N_2 with a five-fold excess of $Cu(OAc)_2$, $Co(OAc)_2$, or $UO_2(OAc)_2$ in H_2O at pH *ca.* 5. Only $UO_2(OAc)_2$ extracted slowly (5 h). The complexes formed§ were one-to-one with no additional ligands.† The complex of Co^{2+} was air sensitive, but those of Cu^{2+} and UO_2^{2+} appeared stable. The complex of UO_2^{2+} was orange, m.p. 153° (decomp.), i.r. (C=O) 1583 cm^{-1}; that of Cu^{2+} was green, m.p. 196° (decomp.), i.r. (C=O) 1580 cm^{-1}; that of Co^{2+} was violet, m.p. 132° (decomp.), i.r. (C=O) 1585 cm^{-1}.

For all ions, the cyclic compounds provided more stable complexes than the open-chain model by factors of between 1·8 and 6·3 powers of ten. For the complexes composed from the divalent ions, the values of log $[K_{av}^{f}$ (cycle)$/K_{av}^{f}$ (model)] decreased in the order, $Ca^{2+} > Mn^{2+} > Cd^{2+} \sim Sr^{2+} > Ba^{2+} > Ni^{2+} > Zn^{2+} \sim Co^{2+} > Mg^{2+} > UO_2^{2+} > Cu^{2+}$, and ranged from 4·7 to 1·8. In general, the higher the value of K_{av}^{f} for the complex between model (**10**) and the divalent cation, the less enhanced the binding of the cycle over the model. With the cyclic (**8**), the dissociation constant for the first proton is the same as that of the model (**10**), but is 2·9 powers of 10 higher than that for the second proton. Thus, when log $[K_{av}$ (**8**)$/K_{av}^{f}$ (**10**)] exceeds 2·9, the extra stability of the cyclic complex is associated with structural factors beyond the simple collection of ligands prior to complexation. The physiologically abundant ions, Ca^{2+}, Mg^{2+}, and Zn^{2+} are bound by (**8**) in substantial amounts at physiological pHs, and (**8**) might serve as an interesting ionophore.[5]

Corey–Pauling–Koltun (CPK) space-filling scale molecular models of the suggested structure (**11**) for these complexes indicate two arrangements that bring six oxygen atoms within ligand-bonding distance. One plane-projected structure describes an **S**, and possesses a centre of symmetry and one C_2 axis. The other describes an **8**, possesses D_2 symmetry, and is chiral.

The pK_as for the first and third protons of (**9**) differ by 4·4 units. The log $[K_{av}^{f}$ (**9**)$/K_{av}^{f}$ (**10**)] value for Ce^{3+} is 6·3, for La^{3+} is 5·9, and for Cr^{3+} is 4·7. The extra stability of the cyclic complexes suggests the ether oxygen atoms also contribute to the binding. CPK models of (**12**) indicate that up to nine oxygen ligands can bond to the metal. One possible arrangement resembles a three-bladed propeller with a C_3 axis.

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