Alkaline-earth Metal Complexes of Macrocyclic Schiff Bases derived from Furan-2,5-dicarbaldehyde

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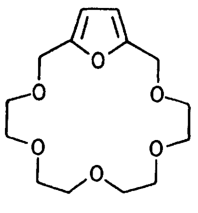
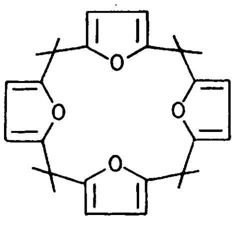
Novel alkaline-earth metal complexes of macrocyclic Schiff bases are formed by the metal-induced condensation of furan-2,5-dicarbaldehyde with 3,6,9-trioxaundecane-1,11-diamine or 1,5-bis(2-aminophenoxy)-3-oxapentane in alcoholic media. In the absence of the metal cation the macrocycles are formed in little or no yield. Magnesium is ineffective in promoting the synthesis of these macrocycles.

CURRENT interest in introducing furan groups into macrocyclic ligands stems from the presence of the furyl unit in naturally occurring antibiotics such as the actins, and the open-chain carboxylic antibiotics as exemplified by X-537A.[1] These antibiotics are known to complex alkaline-earth metal cations and to effect their transport across both natural and artificial membranes.[2-6] The synthesis of model macrocyclic ligands containing furyl groups and the study of their complexing ability could provide useful insight into the much more complex biological processes.

The synthetic macrocycles containing furan units that have been reported are related to polyether ligands. Timko and his co-workers [7,8] have synthesised a wide variety of polyether macrocycles containing furan or tetrahydrofuran moieties by the condensation of furan-2,5-dimethanol with α,ω-ditosylate polyether derivatives to give macrocycles of the type (I). The authors comment that these compounds may act as hosts for the binding of organic and inorganic cations.[7] Simultaneously, Reinhoudt and Gray [9] reported the synthesis of an identical series of ligands and remarked that the yields were considerably increased when the disodium or dipotassium salt of furan-2,5-dimethanol was used, thus invoking an alkali-metal cation template effect. They also reported a study of the complexing of Ziese's salt with ligands such as (I).[10]



(I)



(II)

Template syntheses have also been invoked in the synthesis of the furan-containing macrocycle (II) from the acid-catalysed condensation of furan with acetone in the presence of the perchlorates of Li^+, Ca^{2+}, Mg^{2+}, and Zn^{2+}.[11] In the absence of metal ions the yields are considerably reduced. This reaction has been further investigated by Rest *et al.*,[12] who found that transition-metal salts also gave increased yields, and that perchlorate salts were more effective than chloride salts in yield promotion. They conclude that both the cation and anion are important to the template process because the balance between the size of the cation and anion will determine the degree of dissociation of the metal salt in the reaction media. A related series of macrocycles has been reported by Kobuke *et al.*,[13] who note the ability of these ligands to transport alkali-metal cations across artificial lipid membranes. The complexing ability of these macrocycles towards alkali-metal cations has been studied and a direct relationship established between the stability of the complex and the match between the hole size of the macrocycle and the metal-ion radius.[13]

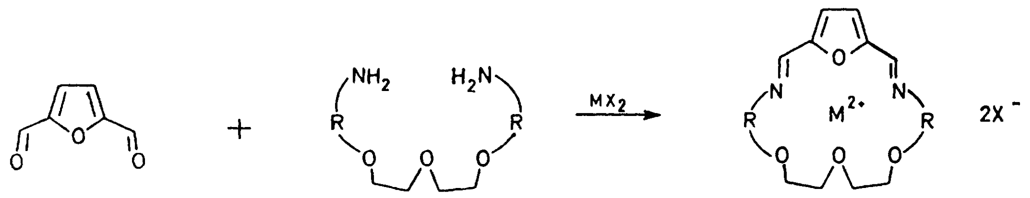
We now report the alkaline-earth metal ion-induced synthesis of furyl-containing Schiff-base macrocycles. A preliminary communication of our work has been presented.[14]

RESULTS AND DISCUSSION

The reaction of furan-2,5-dicarbaldehyde (1) and 3,6,9-trioxaundecane-1,11-diamine (2a) in the presence of alkaline-earth metal thiocyanates or perchlorates, in 1 : 1 : 1 ratio, in a mixture of Bu^nOH and triethylorthoformate and under dinitrogen gave macrocyclic complexes of the type $(3a)\cdot MX_2\cdot nH_2O$. Similarly when (1) and 1,5-bis(2-aminophenoxy)-3-oxapentane (2b) are mixed in ethanol in the presence of the above salts, in a 1 : 1 : 1 ratio, bright orange-yellow precipitates of the macrocyclic complexes $(3b)\cdot MX_2\cdot nH_2O$ result. In contrast, reactions carried out in the presence of Mg^{2+}, or in the absence of metal cation, led to the formation of polymeric materials.

The complexes were characterised by their chemical analyses, i.r. spectra, and where possible mass and ^1H n.m.r. spectra. The formation of cyclic species may be deduced from the absence of carbonyl bands at *ca.* 1 675 cm^{-1} in the i.r. and the presence of imine bands *ca.* 1 630 (3a) and *ca.* 1 615 cm^{-1} (3b). The mass spectral data indicate macrocycle formation since all complexes show a peak corresponding to the free macrocycle and none attributable to higher polymers. In the ^1H n.m.r. there is no resonance corresponding to an aldehyde proton, but a resonance in the 8.26—8.40 p.p.m. region attributable to an imine proton.

Complexes of (3a).—Confirmation of the macrocyclic nature of (3a) comes from the crystal structure of $(3a)\cdot Sr[NCS]_2\cdot H_2O$.[14] This shows the complex to be essentially isostructural with its pyridyl analogue, $(4)\cdot Sr[NCS]_2\cdot H_2O$.[15] The Sr^{2+} is bonded slightly below the plane of the macrocycle and to a strongly co-ordinated water molecule sited above the plane [Sr–O(H_2O) 2.58 Å]. The cation is bonded to all six ring heteroatoms [Sr–O(furan) 2.73, Sr–O(ether) 2.73, Sr–N 2.79 Å] and the anions are '*cis*' *N*-bonded below the macrocyclic plane (Sr–N 2.63 Å). The anions are in slightly different chemical environments, one lying beneath the furyl unit and the other beneath the polyether chain. This, coupled with the different angles subtended at the Sr^{2+} (164.1, 167.5°), accounts for the observed splitting of the ν(C–N) stretching frequency [2 085 and 2 070(sh) cm^{-1}]. The i.r. bonds are similar to those found in the pyridyl analogue.[15,16]

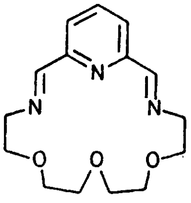


(1)

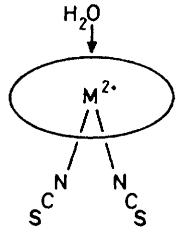
(2a) R = $[CH_2]_2$
(2b) R = o-C_6H_4
M = Ca^{2+}, Sr^{2+}, or Ba^{2+}
X = $[NCS]^-$ or $[ClO_4]^-$

solvent
Bu^nOH — $HC(OEt)_3$ (3a)
EtOH (3b)

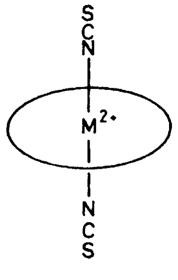
The difficulty of an unambiguous assignment of anion disposition, in complexes of this general type, from i.r. data has been discussed at some length in ref. 16. However, the similarity of (3a) and (4) in the Sr^{2+} complexes may be used to predict structures for the Ca^{2+} and Ba^{2+} species. The complex (4)·$Ba[NCS]_2$·H_2O has been shown to be isostructural with the strontium complex[15] and it is likely that this also pertains to (4)·$Ba[NCS]_2$·H_2O. The i.r. spectrum of this complex is closely similar to that of the Sr^{2+} complex, differing in that a broad single peak is seen at 2 075 cm^{-1}. This feature is also present in the i.r. spectrum of (4)·$Ba[NCS]_2$·H_2O and so a comparable '*cis*' *N*-bonded structure is likely.



(4)



'*cis*' *N*-bonded



'*trans*' *N*-bonded

The complex (3a)·$Ca[NCS]_2$ is anhydrous as is '*trans*' *N*-bonded (4)·$Ca[NCS]_2$.[15] Although in the latter a single ν(C–N) band is seen at 2 065 cm^{-1}, a split ν(C–N) band at 2 065 and 2 055 cm^{-1} appears in the i.r. spectrum of the former. This suggests that, if the direct structural analogy holds, as would be expected on hole size–ion diameter arguments, then it is possible that the angles subtended by the anions at the metal ion in (3a)·$Ca[NCS]_2$ could differ in order to promote inequivalence. Such inequivalence of isothiocyanates has been seen in the related complex {2,15-dimethyl-3,7,10,14,20-pentaazabicyclo[14.3.1]eicosa-1(20),2,14,16,18-pentaene}diisothiocyanatomanganese(II).[17] The i.r. spectrum of (3a)·$Ca[ClO_4]_2$ leads one to suggest that the perchlorate anions are '*trans*' unidentate since the ν_3 bands appear at 1 122 and 1 070 cm^{-1}.[18] In contrast the ν_3 (Cl–O asymmetric stretch) and ν_4 (Cl–O asymmetric bend) bands for the corresponding Sr^{2+} and Ba^{2+} complexes are ambiguous.

The mass spectra of the isothiocyanates follow the trends observed in the pyridyl-containing macrocycles.[16] The complex (3a)·$Ca[NCS]_2$ has as the highest molecular-weight peak $[(3a)\cdot Ca(NCS)]^+$, the strontium complex has $[(3a)\cdot Sr]^+$, and the barium complex has $[(3a)]^+$. With the perchlorates a similar trend is observed but there is also an unusual peak corresponding to $[(3a)\cdot Ca(ClO_4)_2]^+$. The electrical conductances show that all the complexes are 2 : 1 electrolytes in water, whereas in acetonitrile, although the perchlorates are 2 : 1 electrolytes the isothiocyanates are not and show some association. The complex (3a)·$Ca[NCS]_2$ is intermediate between a non-electrolyte and 1 : 1 electrolyte, and the strontium and barium complexes lie between 1 : 1 and 2 : 1 electrolytes. This is seen as a reflection of the stronger co-ordination of the isothiocyanate to the metal, and of its stronger interaction with calcium over strontium and barium.

Complexes of (3b).—The macrocycle (3b) presents a more rigid system imposed by the proximity of the furan ring, imine double bonds, and phenyl rings. The orange-yellow colour of the complexes formed from (3b) indicates that a considerable degree of electron delocalisation occurs in the ring and this is reflected in the low imine band at 1 615 cm^{-1}. The complexes are more insoluble and less crystalline than those of (3a).

The complex (3b)·Ca[NCS]$_2$ exhibits ν(C–N) as a single band at 2 060 cm^{-1} and this is interpreted as indicating adoption of a '*trans*' *N*-bonded structure. The remaining isothiocyanato-complexes are tentatively assigned '*cis*' structures by the comparative arguments used for (3a)·M[NCS]$_2$. The perchlorate complexes exhibit splitting of the ν_3 and ν_4 bands and it is probable that similar structural assignments may be made to those for complexes of (3a). Attempts to prepare (3b)·Ca[ClO$_4$]$_2$ were not altogether successful; although a black microcrystalline product which could be crushed to a yellow-green powder was recovered from the condensation reaction, with an i.r. spectrum consistent with macrocycle formation, an analytically pure sample could not be obtained.

In the mass spectra the highest-molecular-weight peak is that of [(3b)]$^+$ for all six complexes, suggesting a weakened ligation of the metal compared with (3a). The insolubility of the complexes in water limits solution studies. Those that are soluble in acetonitrile parallel the behaviour patterns observed for complexes of (3a).

General Conclusions.—The role of alkaline-earth metal cations in the metal-induced synthesis of furyl-containing macrocyclic Schiff bases has been established. Magnesium does not act as a templating cation for these ligands and this is a further illustration of the cation-size control factor noted previously in the synthesis of comparable pyridyl-containing species.[16,19]

That furan rings are able to participate in template processes may be applicable to the biological syntheses of cyclic antibiotics containing furan rings. If the antibiotic is built up from linear intermediates then it is not unreasonable to propose that alkaline-earth metal cations such as Ca^{2+} might be involved in templating the final cyclisation process, *viz*. the synthesis of corrinoid units [20] where a transition metal is involved in the final co-ordination step.

EXPERIMENTAL

Physical measurements were carried out as described in ref. 16.

Furan-2,5-dicarbaldehyde was prepared by a modification [21] of the method of Oleinik and Novitskii,[22] 3,6,9-trioxaundecane-1,11-diamine by the method of Dietrich *et al.*,[23] and 1,5-bis(2-aminophenoxy)-3-oxapentane by the methods of Tasker and Fleischer [24] and Canon *et al.*[25]

Preparation of the Complexes.—*Di-isothiocyanato*(6,9,12,-20-*tetraoxa*-3,15-*diazabicyclo*[15.2.1]*eicosa*-2,15,17,19-*tetraene*)*calcium*(II), (3a)·Ca[NCS]$_2$. Warm solutions of furan-2,5-dicarbaldehyde (0.124 g, 0.001 mol) and 3,6,9-trioxaundecane-1,11-diamine (0.192 g, 0.001 mol) in n-butanol and calcium thiocyanate (0.200 g of a 78% solution in water, 0.001 mol) were mixed under nitrogen with a few cubic centimetres of triethyl orthoformate. The mixture was warmed and stirred gently for *ca*. 0.5 h after which time the complex had precipitated from solution as an off-white powder. The crude complex was filtered off and recrystallised from ethanol.

All the complexes of (3a) were prepared by a similar procedure; the yields were 40—60%.

Di-isothiocyanato(10,13,16,28-*tetraoxa*-3,23-*diazatetracyclo*[23.2.1.0^{4,9}.0^{17,22}]*octacosa*-2,4,6,8,17,19,21,23,25,27-*decaene*)*calcium*(II), (3b)·Ca[NCS]$_2$. Warm ethanolic solutions of furan-2,5-dicarbaldehyde (0.124 g, 0.001 mol), 1,5-bis(2-aminophenoxy)-3-oxapentane (0.288 g, 0.001 mol), and calcium thiocyanate (0.200 g of a 78% solution in water, 0.001 mol) were mixed and warmed on a steam-bath for *ca*. 10 min. The complex precipitated as a bright orange microcrystalline solid which was purified by warming in ethanol for *ca*. 0.5 h and filtration.

All the complexes of (3b) were prepared by a similar procedure; the yields were 40—60%.

Characterisation data for the complexes are given in Tables 1 and 2.

TABLE 1

Analytical data (%)

Complex	Found			Calculated		
	C	H	N	C	H	N
(3a)·Ca[NCS]$_2$	44.0	4.6	12.4	44.0	4.6	12.8
(3a)·Sr[NCS]$_2$·H$_2$O	38.7	4.3	11.1	38.3	4.4	11.2
(3a)·Ba[NCS]$_2$·H$_2$O	35.1	4.1	10.1	34.8	4.0	10.2
(3a)·Ca[ClO$_4$]$_2$	32.2	3.7	5.4	32.4	3.8	5.4
(3a)·Sr[ClO$_4$]$_2$	29.8	3.5	4.8	29.7	3.5	4.9
(3a)·Ba[ClO$_4$]$_2$·H$_2$O	26.0	3.4	4.3	26.5	3.2	4.4
(3b)·Ca[NCS]$_2$	54.1	3.5	10.5	54.1	3.7	10.5
(3b)·Sr[NCS]$_2$	49.8	3.8	9.7	49.7	3.5	9.7
(3b)·Ba[NCS]$_2$·H$_2$O	44.4	2.7	8.3	44.5	3.4	8.6
(3b)·Sr[ClO$_4$]$_2$	39.7	2.9	4.2	39.8	3.0	4.2
(3b)·Ba[ClO$_4$]$_2$	37.0	2.6	3.8	37.1	2.8	3.9

TABLE 2

Infrared electrical conductance, and mass spectral data

(*a*) Thiocyanato-complexes

Complex	$\tilde{\nu}$(CN)/cm^{-1}	Λ [a]/S cm^2 mol^{-1}		P^+
		H$_2$O	MeCN	
(3a)·Ca[NCS]$_2$	2 065, 2 055	232	65	[(3a)·Ca(NCS)]$^+$
(3a)·Sr[NCS]$_2$·H$_2$O	2 085, 2 070	216	122	[(3a)·Sr]$^+$
(3a)·Ba[NCS]$_2$·H$_2$O	2 075	215	157	[(3a)]$^+$
(3b)·Ca[NCS]$_2$	2 060	[b]	[b]	[(3b)]$^+$
(3b)·Sr[NCS]$_2$	2 092, 2 063	[b]	185	[(3b)]$^+$
(3b)·Ba[NCS]$_2$·H$_2$O	2 060	[b]	[b]	[(3b)]$^+$

(*b*) Perchlorato-complexes

Complex	I.r. bands (cm^{-1})		Λ [a]/S cm^2 mol^{-1}		P^+
	ν_3	ν_4	H$_2$O	MeCN	
(3a)·Ca[ClO$_4$]$_2$	1 122, 1 070		239	283	[(3a)·Ca(ClO$_4$)$_2$]$^+$
(3a)·Sr[ClO$_4$]$_2$	1 145, 1 110, 1 090, 1 067	637, 627, 620	216	294	[(3a)·Sr(ClO$_4$)]$^+$
(3a)·Ba[ClO$_4$]$_2$·H$_2$O	1 100br	630, 625	212	297	[(3a)]$^+$
(3b)·Ca[ClO$_4$]$_2$	1 126, 1 045	645, 637, 620	[b]	[c]	[(3b)]$^+$
(3b)·Sr[ClO$_4$]$_2$	1 120, 1 050	639, 626	[b]	293	[(3b)]$^+$
(3b)·Ba[ClO$_4$]$_2$·H$_2$O	1 100br	638, 628, 610	[b]	284	[(3b)]$^+$

[a] For 10^{-3} mol dm^{-3} solutions at 25 °C. [b] Insoluble. [c] Analytically pure sample unobtainable (see text).

We thank the S.R.C. for an award (to D. H. C.).

[8/783 *Received, 27th April,* 1978]

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