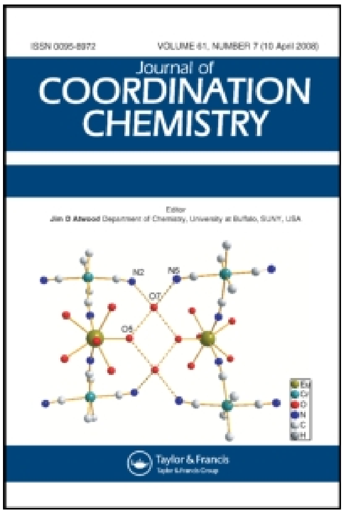

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The template reaction of sodium 2,6-diformyl-4-methylphenolate with alkyl diamines H_2NRNH_2 [$R = (CH_2)_n$, n = 4, 5, 6] led to the production of macrocyclic Schiff bases which were characterized by elemental analyses, IR and proton NMR spectra. Positive ion fast atom bombardment (FAB) and electron spray ionization (ES) mass spectroscopic investigations on the above products showed the presence of a [3 + 3] (H_3L^3) cyclocondensation mode in addition to the common [2 + 2] (H_2L^2) mode. The product in a typical reaction was analysed by capillary electrophoresis (CE) coupled to a mass spectrometer (MS) *via* an electrospray (ES) ionization interface, confirming the independent formation of both tetraimine and hexaimine macrocycles as a mixture of Na_2L^2 and Na_3L^3.

Keywords: Schiff base; macrocycles; sodium template; capillary electrophoresis; electrospray; mass spectra

INTRODUCTION

Complexes of macrocyclic Schiff bases have been extensively studied for the past two decades,[1] since the appearance of Robson's macrocycle capable of binding more than one metal.[2] The employment of these macrocyclic ligands and their analogues has stimulated research in the areas of metallobiosite modelling,[3]

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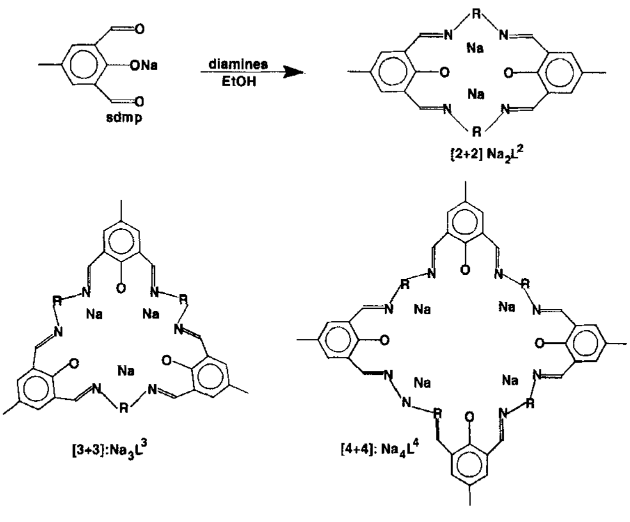
magneto-structural relations,[4] transport and activation of small molecules[5] as well as supramolecular chemistry.[6] Schiff base binucleating macrocyclic ligands derived from [2 + 2] condensation of dicarbonyl precursors and polyamines have been thoroughly investigated for dinuclear systems; however, complexes of [3 + 3] and/or [4 + 4] condensation macrocyclic ligands for polynuclear systems are few because of synthetic difficulty and instability of related macrocycles. In fact, there have been only a few limited instances of [3 + 3] hexaimine Schiff base macrocyclic complexes reported until now,[7] and all these macrocycles have been prepared by template reaction without exception.

We have recently applied a sodium template method for preparing macrocyclic Schiff bases by the reaction of sodium 2,6-diformyl-4-methylphenolate (sdmp) with diamino derivatives and multi-nuclear sodium macrocyclic complexes of [2 + 2] and [2 + 3] cyclocondensation modes have been successfully obtained.[8–9] The related structures have been confirmed by X–ray crystallography of transition metal complexes obtained *via* transmetallation.[9] Here report the synthesis, FAB and ES mass spectroscopic characterisation of the [3 + 3] mode derived from the macrocyclic Schiff base condensation of sdmp with alkyl diamines, of which products in a typical reaction are analysed by an on-line CE/ES-MS technique. The synthetic reaction is illustrated in Figure 1.



Reaction	R
1	$(CH_2)_4$
2	$(CH_2)_5$
3	$(CH_2)_6$

FIGURE 1 Synthetic reactions.

EXPERIMENTAL

Instruments and Chemicals

Elemental analyses were carried out by the Analytical Centre service of Nanjing University. Infrared spectra were recorded in KBr pellets with a 170SX Fourier-Transform infrared spectrophotometer. Proton NMR spectra were recorded on solutions in CD_3OD using a Bruker 250 MHz NMR spectrometer with TMS as internal reference. Positive FAB mass spectra were measured utilizing a VG–2AB–HS mass spectrometer with NOBA as the matrix solvent. Capillary electrophoretic separation was undertaken on a Beckman P/ACE 5000 capillary electrophoresis instrument, 80 cm from inlet to MS apparatus. Electronspray ionization mass spectra were recorded on a Finnigan MAT SSQ 710 mass spectrometer with scan range of 400–1000 amu. The preparation of sodium 2,6-diformyl-4-methylphenolate (sdmp) has been described previously.[8] All amines were commercial products and used as received.

Synthesis of Macrocyclic Products

The condensation was carried out using a general procedure. To a suspension of sdmp (1 mmol) in absolute ethanol (20 cm^3) an equimolar amount of the corresponding diamine in ethanolic solution (10 cm^3) was added. The mixed solution was kept stirring at room temperature and it gradually became clear. After 3 h, the resulting yellow solution was filtered to remove insoluble impurities. Then the filtrate was concentrated on a rotary evaporator and ether was added until a great deal of solids deposited. The product was collected and dried *in vacuo*. It is noted that all substances obtained in reactions **1** – **3** should be kept in a vacuum desiccator over P_2O_5, because they slowly gain weight when exposed to air. Each product has been characterised by microanalyses, infrared and ^1H NMR spectra. **1**. *Anal.* Calcd for $C_{39}H_{45}N_6O_3Na_3 \cdot 6H_2O$ (%): C, 56.9; H, 6.9; N, 10.4. Found: C, 56.7; H, 7,0; N, 10.4. IR (KBr disc, cm^{-1}): 3421 (br, ν_{OH}), 1636 (s, $\nu_{C=N}$); ^1H NMR (δ ppm): 8.62 (s, CH=N), 7.46 (s, ArH_2), 3.63 (t, $NCH^*_2CH_2CH_2CH^*_2N$), 2.24 (s, $ArCH_3$),1.83 (m, $NCH_2CH^*_2CH^*_2CH_2N$), area ratio: 2:2:4:3:4. **2**. *Anal.* Calcd for $C_{42}H_{51}N_6O_3Na_3 \cdot 7H_2O$ (%): C, 57.1; H, 7.4; N, 9.5. Found: C, 57.2; H, 7.2; N, 9.4. IR (KBr disc, cm^{-1}): 3420 (br, ν_{OH}), 1637 (s, $\nu_{C=N}$); ^1H NMR (δ ppm): 8.48 (s, CH=N), 7.42 (s, ArH_2), 3.68 (t, $NCH^*_2CH_2CH_2CH_2CH^*_2N$), 2.17 (s, $ArCH_3$), 1.78 (m, $NCH_2CH^*_2CH_2CH^*_2CH_2N$), 1.34 (m, $NCH_2CH_2CH^*_2CH_2CH_2N$), area ratio: 2:2:4:3:4:2. **3**. *Anal.* Calcd for $C_{45}H_{57}N_6O_3Na_3 \cdot 9H_2O$ (%): C, 56.5; H, 7.9; N, 8.8. Found: C, 56.1; H, 7.6; N, 9.0. IR (KBr disc, cm^{-1}): 3421 (br, ν_{OH}), 1637 (s, $\nu_{C=N}$).

RESULTS AND DISCUSSION

Sodium ion, the template, was especially introduced to the cyclocondensation as the dicarbonyl precursor salt instead of as an inorganic metal salt. Reaction was carried out by mixing equimolar sdmp and the corresponding diamine in absolute ethanol under mild conditions. The infrared spectra of all products showed no absorption ascribed to $\nu_{(C=O)}$ bands near 1680 cm^{-1} compared with that of sdmp, but gave strong absorptions near 1636 cm^{-1} assigned to $\nu_{(C=N)}$ bands, indicative of the presence of Schiff bases. Crystalline water was observed in each IR spectrum. Due to low solubility in either organic solvents or water, not all samples gave good ^{1}H-NMR spectra for analysis; only products in reactions **1** and **2** in CD_3OD have signals strong enough to be identified. In these two spectra, peaks attributed to imine groups have been observed, while peaks corresponding to CHO groups in the starting material have not been found, demonstrating the Schiff base linkage as well. Since all substances are hygroscopic, they increase in weight during microanalytical measurements. Analytical data are not consistent with theoretical values until crystalline water is included. Although infrared and ^{1}H NMR data as well as elemental analyses have provided useful information on the formation of Schiff bases, the cyclocondensation mode can not be determined on the basis of the above data.

In order to define whether these Schiff bases are products of [2 + 2], [3 + 3] or [4 + 4] cyclocondensation modes, positive FAB mass spectra of each product were measured. The main FAB-MS peaks are assigned and listed in Table I and a typical spectrum is shown in Figure 2. Both [2 + 2] and [3 + 3] modes are observed in each spectrum as fragments of sodium-containing macrocycles and free macrocyclic ligands. In comparison with the FAB mass spectra, the ES mass spectrum of the product in reaction **2** was also recorded and is given in Figure 3. $[H_3L^2]^+$ (*m/z* 461) and $[NaH_2L^2]^+$ (*m/z* 483) species of the [2 + 2] mode were observed, similar to that of the corresponding FAB-MS. Meanwhile, the parent molecular peak of the [2 + 2] mode appeared as $[Na_2HL^2]^+$ at *m/z* 505 with low abundance. While for the [3 + 3] mode only a signal at *m/z* 691 attributed to $[H_4L^3]^+$ was found, $[NaH_3L^3]^+$ was not observed in contrast to the compatible FAB–MS spectrum. Both FAB and ES mass spectra can give useful structural information; however, they can not give details about whether products in these reactions are mixtures or pure compounds and whether they are stable under FAB or ES–MS conditions in which [2 + 2] and [3 + 3] cyclocondensation modes exist as a blend. In addition, splitting patterns of high grade modes may cover those of low grade ones. For further study, the product in reaction **2** was separated by a capillary electrophoretic method and was analysed by an on-line ES ionization mass spectrometer interfaced with the CE apparatus.

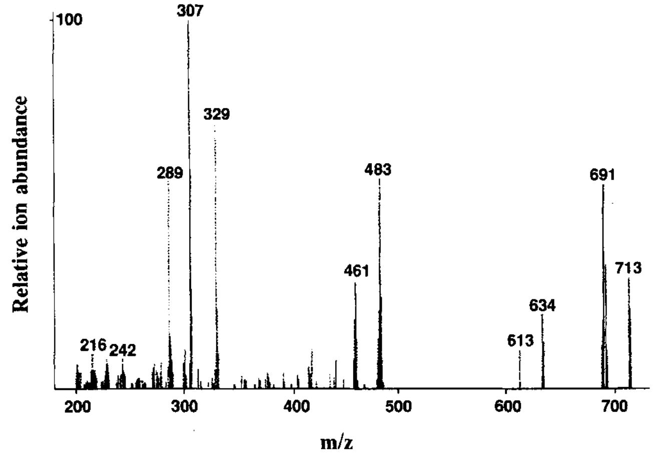


FIGURE 2 The FAB mass spectrum of products in reaction 2.

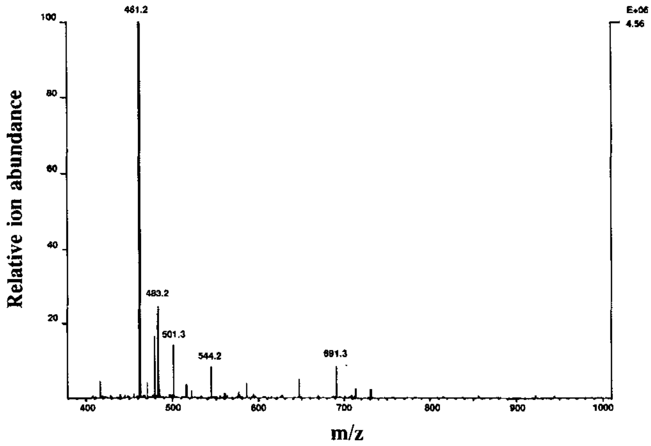


FIGURE 3 The ES ionization mass spectrum of products in reaction 2 (solvent acetylnitrile/water = 1 :1 v/v).

TABLE I Principal FAB-MS peaks (*m/z*) of products in reactions **1** - **3** with abundances (%) in parentheses*

Type	*m/z*	*1*	*2*	*3*
[2+2]	Mw(Na_2L^2)	476	504	532
	$[NaH_2L^2]^+$	455(32)	483(57)	511(14)
	$[H_3L^2]^+$	433(100)	461(28)	489(32)
[3+3]	Mw(Na_3L^3)	714	756	798
	$[NaH_3L^3]^+$		713(29)	
	$[H_4L^3]^+$	649(20)	691(53)	733(13)

*[2+2] and [3+3] Macrocyclic Schiff bases are abbreviated as H_2L^2 and H_3L^3, respectively.

The reconstructed ion current (RIC), the total intensity of a scan with a sum of all the individual signals (currents) associated with each ion in the spectrum, is plotted in Figure 4, and the relative single ion current is displayed in Figure 5. Plots of the RIC against scan number (80~200) show two main signals at *m/z* 461 ($[H_3L^2]^+$) and *m/z* 691 ($[H_4L^3]^+$), indicative of a constituent separation. The on-line ES-MS examination of the isolated components demonstrates the independent presence of [2 + 2] and [3 + 3] macrocycles (Figure 6). The area ratio between tetraimine and hexaimine macrocycles is approximately 7 to 1, and thus the [2 + 2] cyclocondensation mode is the major product in the reaction. It is obvious that the obtained macrocycles are stable under soft-ionization conditions as in FAB-MS and ES-MS. Based on the CE/ES-MS analysis, it is reasonable to conclude that each product in the corresponding reaction is a mixture of Na_2L^2 and Na_3L^3. Moreover, it is impossible for high grade condensation modes, *e.g.* [4 + 4] or [3 + 3] macrocyclic Schiff bases, to split into fragments of the corresponding low grade modes under the conditions that FAB or ES ionization mass spectra are measured. Consequently, splitting of each mode in the FAB and ES mass spectra is similar to those of [2 + 2] and [2 + 3] modes, [8, 10] which can be summarized in the following scheme:

$$Na_n\,L^n \xrightarrow{H^+} [Na_n\,L^n\,H]^+ \xrightarrow[-Na^+]{H^+} [Na_{n-1}\,L^nH_2]^+ \longrightarrow \ldots \xrightarrow[-Na^+]{H^+} [L^n\,H_{n+1}]^+$$

where n is a cyclocondensation mode. It is of interest to note that the loss of a sodium cation from the molecular species under FAB conditions would generate a proton to add in, despite the fact that not all the corresponding species can be observed in their mass spectra.

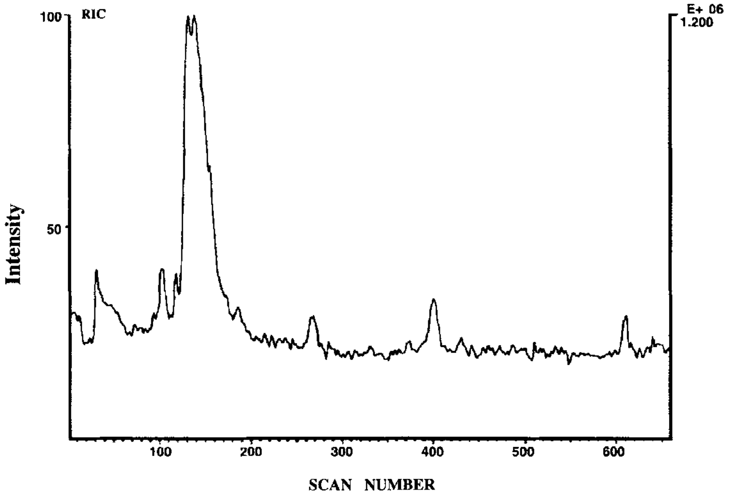


FIGURE 4 A CE/ES-MS RIC diagram of products in reaction 2 (conditions as described in Figure 5).

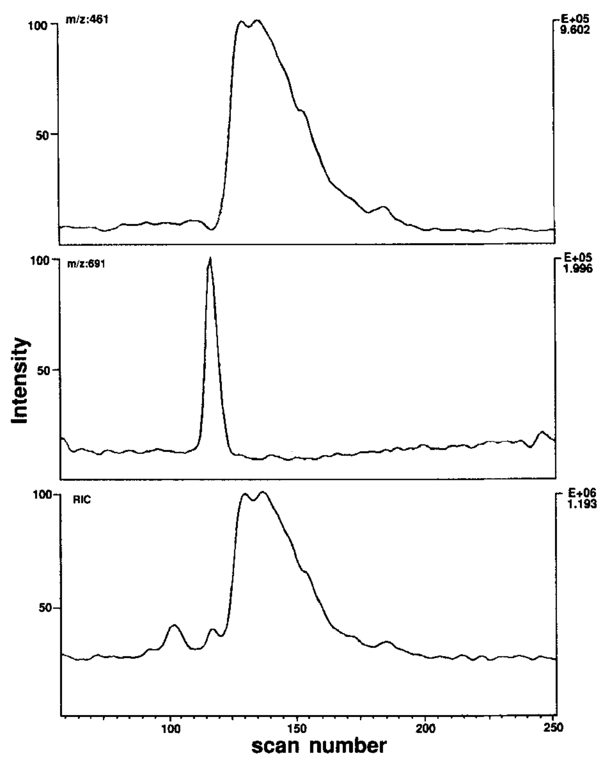


FIGURE 5 Single ion electropherograms of on-line CE/ES-MS analysis of the isolated components in reaction 2. Capillary was uncoated, fused silica, 80cm × 75μm i.d.; separation buffer, 0.1 mM HOAc; separation voltage 30 kV, ES voltage 4.5 kV, sheath liquid isopropanol:water:acetic acid (60:40:1 v/v/v) delivered at 3μl/min, scan range 400–1000 amu, mass spectrometer resolution ≈ 1000.

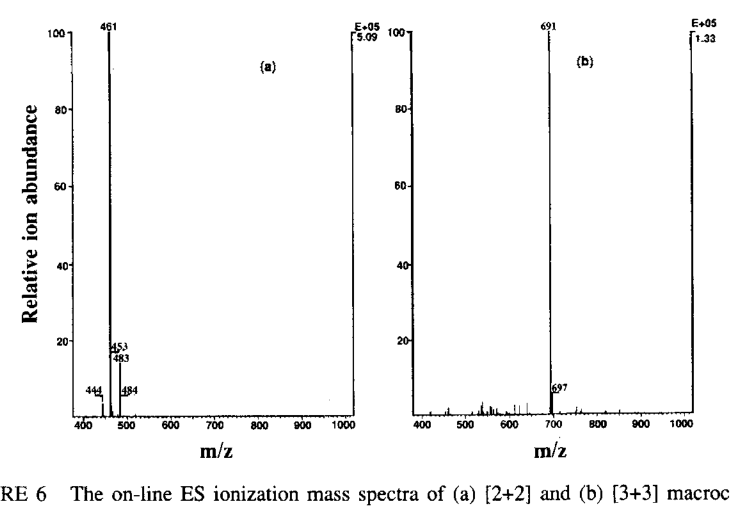


FIGURE 6 The on-line ES ionization mass spectra of (a) [2+2] and (b) [3+3] macrocycles.

Generally, the formation of the most common [2 + 2] macrocyclic Schiff bases has been reported by template cyclocondensation,[1] although there are sparse references to macrocyclic Schiff base ligands being synthesized by the direct condensation of dicarbonyl precursors and polyamines in the absence of metal ions.[11] However, there has been no evidence so far that [3 + 3] or [4 + 4] macrocycles can be prepared by non-template procedures (in which polymer–like oil or resin is usually obtained). Alkali metals as template have been previously utilized in the synthesis of crown ethers and relative compounds.[12] They are seldom involved in the preparation of macrocyclic Schiff bases. Sodium template here, the combination of a conventional template and a precursor, plays a unique role in the generation of macrocyclic Schiff bases. It has been noticed that only diamines with polymethylene chains, $(CH_2)_n$ ($n \geq 4$, when $n = 3$, the [2 + 2] mode is readily produced due to the high stability of the macrocycle), have led to the production of [3 + 3] macrocycles. If there is a heteroatom such as O or N in the methylene chain, a [2 + 2] mode will generally occur.[8] Further research on the synthesis and isolation of [3 + 3] or [4 + 4] modes by chemical means needs to be undertaken for this template reaction.

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