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Microwave assisted cyclocondensation of dialdehydes with chiral diamines forming calixsalen type macrocycles

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Abstract—Microwave irradiation of various dialdehydes and chiral diamines afforded chiral macrocyclic imines in moderate to good yields. Linked dialdehydes predominantly form [2+2] macrocycles whereas dialdehydes without linkers yield [3+3] macrocycles. This is the first report of template-free synthesis of calixsalen-type macrocycles formed in shorter reaction times under microwave conditions. In all the reactions, the salts of chiral diamines were used in contrast to the free diamines normally employed.

Over the past few decades, macrocyclic compounds have been extensively studied for their molecular recognition and supramolecular structures. Macrocycles containing a Schiff base and hydroxyl moieties[1] are particularly attractive as they form multi-metal complexes which exhibit catalytic and fluorescent properties.[2] Gawronski et al.[3] introduced a synthetic strategy for the synthesis of chiral macrocyclic hexaimines via a [3+3] cyclocondensation of 1,4- and 1,3-dialdehydes and enantiopure diamines under dilute reaction conditions. Kuhnert et al.[4] have synthesized similar chiral macrocycles containing up to 42-membered rings using a variety of dialdehydes. Indeed, many examples of macrocyclic polyimines formed by [2+2] and [3+3] cyclocondensation reactions are known.[5] Jablonski and co-workers[6] synthesized hydroxyl-containing [2+2] chiral macrocyclic calixsalens using a metal ion template. Apart from applications in supramolecular chemistry, these macrocyclic salen compounds are also used as fluorescent sensors[2] and as chiral ligands for a variety of asymmetric catalytic reactions like epoxidation,[6a] alkyne addition[7] and epoxide ring-opening reactions.[8] Jacobsen et al.[8] employed a chiral cyclic oligosalen ligand, which is an oligomeric mixture, for asymmetric epoxide ring-opening reactions. Although many examples of chiral macrocyclic Schiff bases have been reported, a short and efficient synthesis of this type of macromolecule remains a challenge for synthetic chemists since the existing methods involve the need for a template, dilute reaction conditions, long reaction times and enantiomerically pure diamines.

Herein, we report the first synthesis of calixsalen type chiral macrocyclic polyimines using salts of cyclic as well as acyclic diamines under microwave irradiations. The reaction is very rapid and does not require harsh conditions.

Scheme 1 represents the general procedure for the formation of calixsalen type macrocycles from linked dialdehydes and chiral diamines. The process involves microwave irradiation (unmodified domestic microwave oven) of a mixture containing the dialdehyde and the salt of a chiral diamine with an excess of potassium carbonate in 1:1 water–ethanol for 5 min (the corresponding thermal reaction takes 2–3 h which predominantly forms linear polymers with lower yield of macrocycles).

Condensation of 5,5′-methylene-bis-salicylaldehyde[6a] **1** with (1*R*,2*R*)-diammoniumcyclohexane mono-(+)-tartrate[9a] **2** gave a mixture of [1+1], [2+2] and [3+3] cyclocondensation products in 55% yield (Table 1, entry 1). The MALDI-TOF spectra of this mixture clearly showed predominant peaks due to [1+1], [2+2] and [3+3] macrocycles (*m*/*z* 334, 668, and 1002). These macrocycles were analyzed as a mixture and the individual components were not isolated. With a cyclic diamine

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Keywords: Macrocycles; Schiff bases; Microwave.

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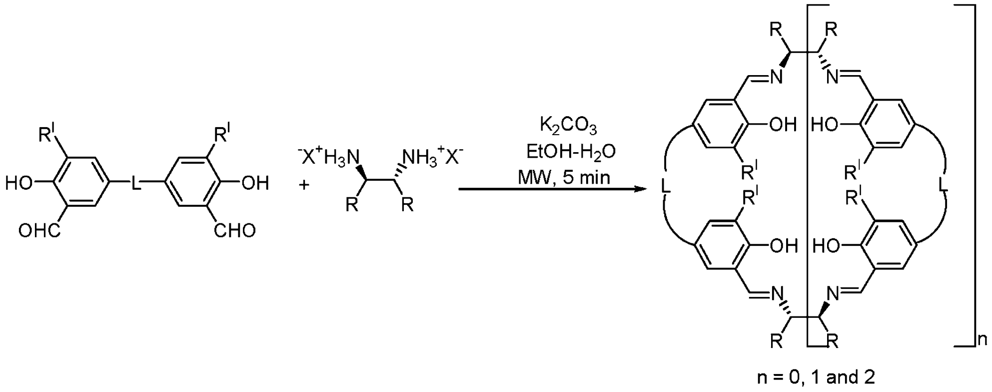


Scheme 1. Cyclocondensation of linked dialdehydes with chiral diamines under microwave irradiation.

Table 1. [2+2] Cyclocondensation of linked dialdehydes with chiral diamines

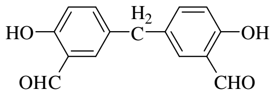
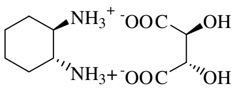
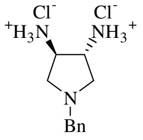
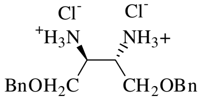
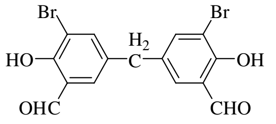
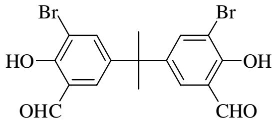
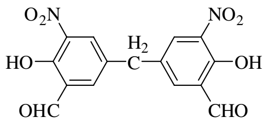
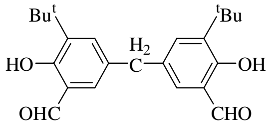
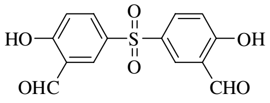
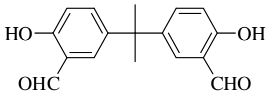
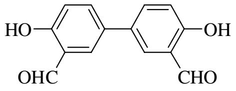
Entry	Dialdehyde	Chiral diamine	Yield (%)
1	 **1**	 **2**	55[a]
2		 **3**	31[b]
3		 **4**	26[b]
4	 **5**	**2**	45[b]
5		**3**	52[b]
6	 **6**	**2**	41[b]
7		**3**	47[b]
8	 **7**	**2**	ND
9	 **8**	**4**	25[b]

Table 1 (*continued*)

Entry	Dialdehyde	Chiral diamine	Yield (%)
10	 **9**	**2**	47[b]
11	 **10**	**2**	78[a]
12	 **11**	**2**	36[b]

ND = not determined.

[a] Isolated yields of a mixture of macrocycles.

[b] Isolated yield of [2+2] macrocycle.

derived from L-(+)-tartaric acid, namely (3*R*,4*R*)-diamino-1-benzylpyrrolidine hydrochloride[9b] **3**, the [2+2] macrocycle was isolated in 31% yield (Table 1, entry 2). However, in the case of condensation between **1** and an acylic diamine, derived from L-(+)-tartaric acid, namely (2*R*,3*R*)-1,4-bis(benzyloxy)-2,3-diaminobutane hydrochloride[9c] **4**, the [2+2] cyclocondensed imine (*m*/*z* 1040) was isolated in 26% yield (Table 1, entry 3). The low yields in most of these cases was due to the formation of linear oligomeric imines. All polycyclic imines displayed the predicted spectroscopic features, most importantly one set of NMR signals indicating a highly symmetric structure.

Using similar reaction conditions, a variety of bromo functionalized [2+2] macrocyclic Schiff bases were synthesized for the first time in good yields. Unlike other dialdehydes, these bromo dialdehydes required a large excess of ethanol for complete solubility and hence these reactions were performed under dilute conditions. Microwave irradiation of (1*R*,2*R*)-**2** and (3*R*,4*R*)-**3** gave the [2+2] macrocyclic imines as the only isolated products with the dialdehydes 5,5′-methylene-di-3-bromosalicylaldehyde[10a] **5** and 5,5′-methylethylidene-di-3-bromosalicylaldehyde **6** (Table 1, entries 4 to 7). Microwave irradiation of 5,5′-methylene-di-3-nitrosalicylaldehyde[10b] **7** and (1*R*,2*R*)-**2** (Table 1, entry 8) produced a Schiff base which was soluble only in DMSO, which limited its purification and characterization.

The condensation between the substituted dialdehyde 5,5′-methylene-di-3-*tert*-butyl-salicylaldehyde[6a] **8** and (1*R*,2*R*)-**2** under thermal conditions is known to form linear polymers.[11] However, under microwave irradiation, two major products were formed, the [2+2] macrocyclic imine and the corresponding [2+1] linear oligomer in 83% overall yield. In contrast, (2*R*, 3*R*)-**4** yielded a [2+2] macrocyclic Schiff base as the only macrocycle in 25% yield (Table 1, entry 9). A similar trend was observed in the case of cyclocondensation of 5,5′-methylene-di-3-*iso*-propylsalicylaldehyde[6a] and (1*R*,2*R*)-**2** which produced a mixture of the [2+2] macrocycle and the [2+1] linear oligomer in 86% overall yield.

The dialdehyde 5,5′-sulfonyl-*bis*-salicylaldehyde[10c] **9**, formed the [2+2] macrocyclic imine as the only cyclized product in good yield with (1*R*,2*R*)-**2** (Table 1, entry 10). However, (1*R*,2*R*)-**2**, when treated with 5,5′-methylethylidene-bis-salicylaldehyde[10d] **10** resulted in a mixture of [1+1], [2+2] and [3+3] cyclocondensed products in 78% yield (Table 1, entry 11).

Interestingly, the cyclocondensation of 5,5′-bis-salicylaldehyde[10e] **11** (Table 1, entry 12) with (1*R*,2*R*)-**2** resulted in the isolation of two main products that were identified by MALDI-TOF measurements (*m*/*z* 640, 1920). The ions correspond to 24-membered [2+2] and 72-membered [6+6] macrocycles.

In contrast to linked dialdehydes, a dialdehyde without a linker condensed with a chiral diamine to give a [3+3] macrocyclic hexaimine (Fig. 1). 2,5-Dihydroxyterephthalaldehyde[10f] **12** condensed under microwave irradiation with (1*R*,2*R*)-**2** in a short reaction time to give the [3+3] macrocycle **A** in excellent yield (Table 2, entry 1). The X-ray crystallographic analysis[12] of the macrocycle **A** grown from an acetonitrile–dichloromethane solution confirmed the cyclic nature of the structure (Fig. 2). The compound has a triangular shape with three diaminocyclohexyl moieties at the apex and a molecule of ethanol trapped at the center of the macrocycle. Each hydroxyl group points towards the nitrogen of an imine indicating a strong intramolecular hydrogen bond network. No intermolecular hydrogen bonds were observed.

However, reaction of (2*R*,3*R*)-**4** with **12** gave the [3+3] macrocycle **B** in 42% yield (Table 2, entry 2). Again, the yield in this case was moderate due to the formation of linear oligomers as byproducts.

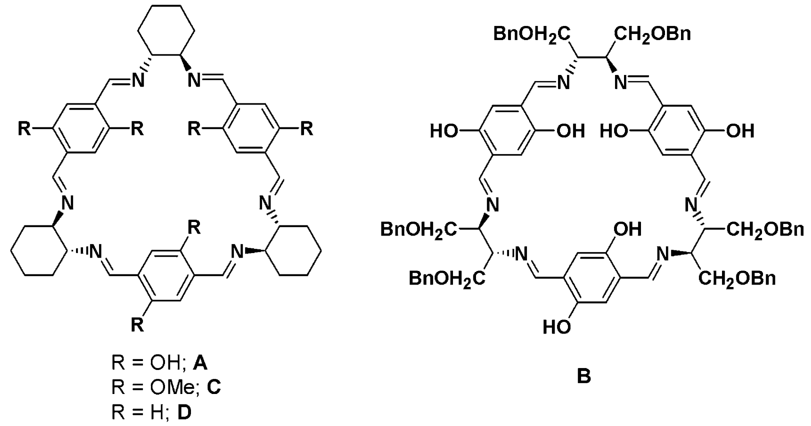
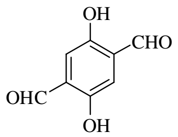
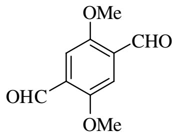
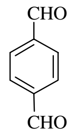


Figure 1. Structures of [3+3] cyclocondensed macrocycles.

Table 2. [3+3] Cyclocondensation between dialdehydes without linkers and chiral diamines

Entry	Dialdehyde	Chiral diamine	Yield (%)[a]
1	 **12**	2	94
2		4	42
3	 **13**	2	82
4	 **14**	2	90

[a] Isolated yield of [3+3] macrocycle.

Since the phenolic group assists the cyclization reaction, we wanted to check the feasibility of forming macrocycles with dialdehydes which did not contain phenolic groups, for example, 2,5-dimethoxyterephthalaldehyde[10f] **13** and terephthalaldehyde **14**. On reaction with (1*R*,2*R*)-**2** we found that both dialdehydes produced the [3+3] macrocyclic imines, **C** and **D**, as the major products in good yields (Table 2, entries 3 and 4).

In summary, we report an efficient and template-free synthesis of calixsalen type macrocycles in short reaction times.

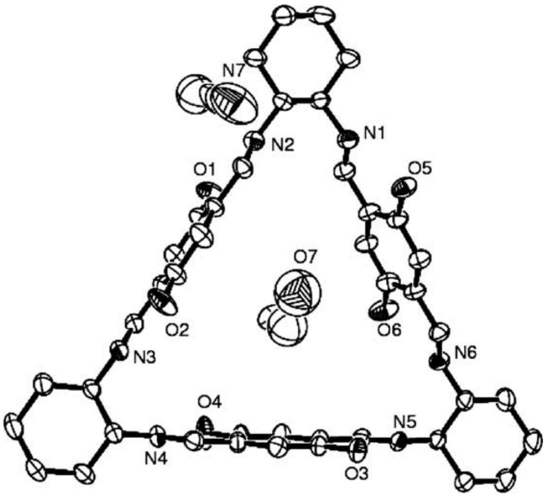


Figure 2. ORTEP (50% ellipsoid) plot of macrocycle **A** $C_{42}H_{48}N_6O_6$·EtOH·CH_3CN. Carbons are unlabelled and hydrogens are omitted for clarity.

Typical experimental procedure: To a solution of (1*R*,2*R*)-diammoniumcyclohexane mono-(+)-tartrate **2** (191 mg, 0.723 mmol) and K_2CO_3 (200 mg, 1.45 mmol) in 1 mL of water was added a solution of 2,5-dihydroxyterephthalaldehyde **12** (100 mg, 0.602 mmol) in 1 mL of ethanol. This homogeneous mixture was irradiated in an unmodified domestic microwave oven at low power setting for 5 min. The reaction mixture was cooled to room temperature and the solid material formed was filtered off. The solid material was dissolved in ethyl acetate and the undissolved material was removed by filtration. The filtrate was dried over sodium sulfate, concentrated under reduced pressure and the crude product was purified by column chromatography over silica gel using 20% EtOAc–hexane to afford pure yellow [3+3] macrocyclic hexamine **A** (140 mg, 94%). Mp: >300 °C $[\alpha]_D^{28}$ −642 (*c* 1.0, CH_2Cl_2); IR (KBr) *v* 3433, 1625 cm^{-1}; ^1H NMR ($CDCl_3$): *δ* 1.46 (s, 6H), 1.70–1.72 (m, 6H), 1.88 (s, 12H), 3.22–3.31 (m, 6H), 6.70 (s, 6H), 8.18 (s, 6H), 12.29 (s, 6H); ^{13}C NMR ($CDCl_3$): *δ* 24.2, 32.9, 73.8, 118.4, 121.0, 152.5, 163.9; MALDI-TOF-MS: *m*/*z* 733 ($[M+H]^+$). Anal. Calcd for $C_{42}H_{48}N_6O_6$·C_2H_6O: C, 67.85; H, 6.98; N, 10.79%. Found: C, 67.72; H, 6.75; N, 10.23%.

Acknowledgements

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12. Crystal data for **A** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 262613, $C_{46}H_{57}N_7O_7$, reddish-orange crystal, monoclinic, space group $P21$ (no.), a = 14.326 (4), b = 9.186 (3), c = 18.677 (4) Å, V = 2331.0 (11) $Å^3$, Z = 2, d_{calcd} = 1.168 mg m^{-3}, T = 293 (2) K, Enraf Nonius CAD4 diffractometer, Mo-K_α (λ = 0.71069 Å), μ = 0.080 mm^{-1}, collected reflections 4534, unique 4353 (R_{int} = 0.0313), $2\theta_{\max}$ = 24.97°, Final R indices [$I > 2\sigma$ (I)]: R_1 (observed) = 0.0563, wR_2 = 0.1567, R (all data): R_1 = 0.1234, wR_2 = 0.1950, GOF(F^2) = 1.022.