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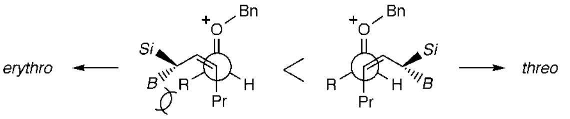

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Organoclay Derivatives in the Synthesis of Macrocycles

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The synthesis of macrocyclic systems is profoundly hindered by reactions of participating components that lead to the formation of mainly oligomeric or polymeric compounds. To overcome this deficiency, template-assisted methods based on metal coordination, electron-donor interactions, hydrogen bonding, and electrostatic interactions have been successfully developed.[1] In these reactions the templating agent plays the essential role of assembling and organizing the participating molecules in a way that makes possible a desirable reaction pathway that would not occur in its absence.[2]

Another potential approach to effectively assemble and organize compounds into well-defined supramolecular arrays

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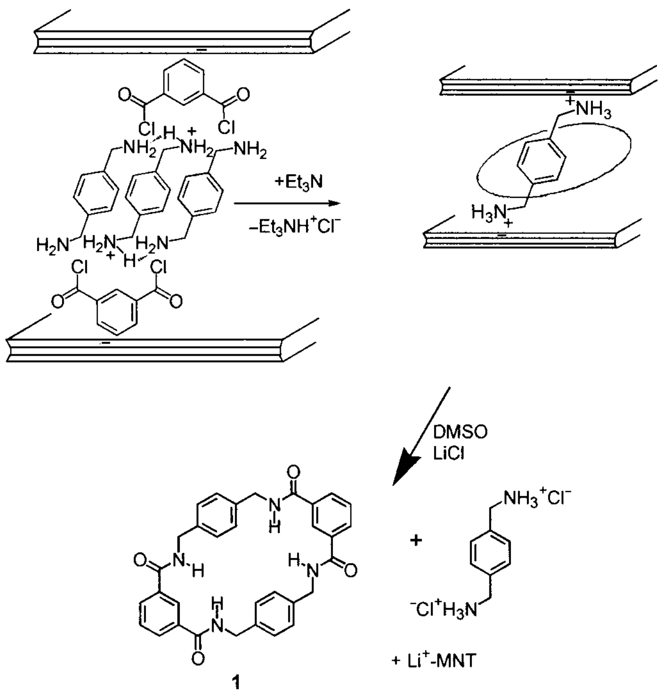
is to exploit the intercalation properties of layered solids. Towards this aim, we demonstrate herein that host–guest interactions in lamellar solids offer the means to manipulate the synthesis of macrocycles in a controllable manner.

The host lamellar solid used in our work belongs to the family of 2:1 mica-type layered aluminosilicate minerals and, in particular, to the minerals known as smectite clays. Smectites possess unique swelling, intercalation, and ion-exchange properties that enable their transformation into various classes of derivatives.[3] One such class of easily accessible derivatives results from the uniform insertion of organic cations at the exchange sites of the mineral.[4] A main feature of these organoclay solids is the efficient orientation and alignment of the organic cations in the interlayer zone or galleries of the clay. Apparently, such properties are highly desirable for the active engagement of clay surfaces as templates in the synthesis of macrocycles bearing basic nitrogen substituents.

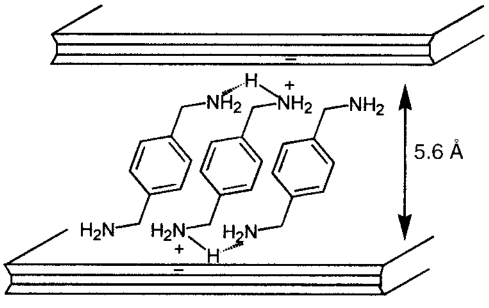
As an application of these concepts we report the successful synthesis of the tetraamido macrocycle **1** (Scheme 1) on the clay surfaces. The original attempt to synthesize this molecule by direct condensation of *p*-xylylenediamine with isophthaloyl dichloride in $CHCl_3$ gave a [2]-catenane (two interlocked units) as the only isolable product together with other cyclic oligomers and polymers.[5] The macrocycle was successfully synthesized in the form of a rotaxane (28% yield) by the same condensation reaction in the presence of a five-unit molecular axle.[6]



Scheme 1. Proposed pathway for the intergallery formation of macrocycle **1** (– denotes the negative charge of the clay layers).

Our synthetic approach to **1** employed the following four steps: a) preparation of a pillared clay from the dihydrochloride salt of *p*-xylylenediamine, b) insertion of neutral *p*-xylylenediamine into the pillared structure, c) reaction of the neutral *p*-xylylenediamine in the layers with the isophthaloyl chloride and formation of the tetramide macrocycle, and d) extraction of the product from the clay.

The first step involves the insertion of the diprotonated *p*-xylylenediamine between the clay layers to give a pillared clay (product **a**) with a basal spacing d_{001} of 13 Å. This distance suggests that there is a single layer of diamine dications lying flat between the clay surfaces. The next step is the introduction of neutral *p*-xylylenediamine into the galleries of the pillared clay. The new organoclay composite (product **b**) was obtained by the addition of a solution of the *p*-xylylenediamine in water (twice the cation-exchange capacity) to a suspension of the pillared clay. The product gave an X-ray diffraction (XRD) pattern with a d_{001} spacing of 15.1 Å. The higher d spacing suggests that the insertion of the neutral diamine into the layers forces the intercalated diamine to adopt a lifted position. Such a position can be explained by assuming that the insertion of diamine between the layers creates an aggregated or a hemisalt structure that arises from hydrogen bonding between the protonated and neutral amino groups (Scheme 2). Similar hemisalt associations in clays has been reported for other amines[7] and diamines.[8] Furthermore, after washing **b** with water the d spacing returned to 13 Å, which suggests that the neutral diamine is only weakly held in the layers and therefore is easily eluted into the water phase, leaving behind the protonated diamine cations in a flat orientation. Additional evidence for an interlayer hemisalt formation derives from the FT-IR spectrum of product **b** (Figure 1). The third step is the reaction of isophthaloyl dichloride with a suspension of **b** in CH_3CN in the presence of Et_3N. The intergallery condensation was carried out at room temperature by stirring the suspension for a few hours. The interlayer formation of the cyclic tetramide **1** in Scheme 1 was confirmed by ^1H NMR and FT-IR spectroscopies. The ^1H NMR spectrum[9] contained all the characteristic peaks reported for the authentic macrocycle in the literature[6a] and additional peaks related to the diamine dication pillars. The FT-IR spectrum of the interlayered macrocycle showed the typical amide bands at 1530 and 1635 cm^{-1}. In addition, a strong band at 3000 cm^{-1} indicates that the diamine dications are still maintained in the clay layers, whereas the hydrogen bonds that identify the hemisalt formation have disappeared.



Scheme 2. Schematic representation of the intergallery *p*-xylylenediamine hemisalt formation (– denotes the negative charge of the clay layers).

A schematic illustration of the reaction pathway which complies with the observed results is depicted in Scheme 1.

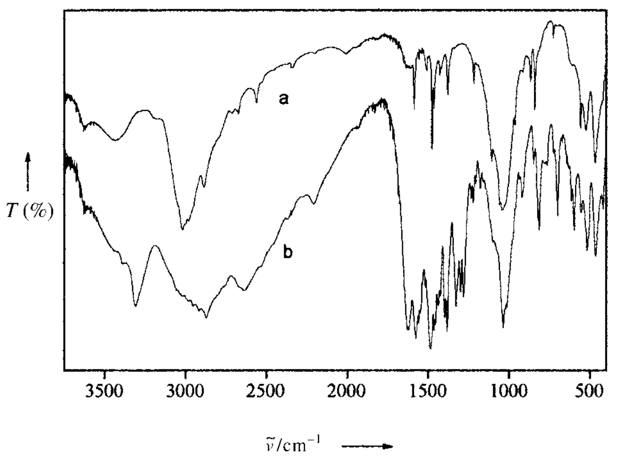


Figure 1. FT-IR spectra (KBr) of: a) the pillared clay (product **a**), b) the clay with the hemisalt in the interlayer space after the intercalation of pillared clay with the neutral diamine (product **b**). The characteristic broad band between 3300–2200 cm^{-1} arising from the $[H_2N\text{-}H\cdots NH_2]^+$ hemisalt grouping is replaced in **a** by a strong band near 3000 cm^{-1} which arises from the electrostatically bound $[H_3NCH_2C_4H_4CH_2NH_3]^{2+}$ ions. The spectra are different in the region between 1700–1300 cm^{-1} which is associated with the NH_2 scissoring vibrations and the NH_3^+ symmetric deformations.

The isophthaloyl chloride enters the interlayer zone during the synthesis and reacts with the aligned, in-register hydrogen-bonded diamine components to produce the cyclic tetramide. The mode of tetramide formation dictates the wrapping of the molecule around the dicationic organic pillar. The situation is analogous to a rotaxane system, with the mineral layers taking the place of the dumbbell stoppers. Furthermore, the molecular axle, that is, the organic pillar, is rigid and prefixed in the mineral layers. In agreement with the rigid diamine axle, the XRD pattern of the resulting complex shows a basal spacing at 15 Å, which implies that the organic dications maintain their upright position. The interlocked state of the tetramide makes its removal from the clay layers very difficult or even not possible. In fact, although the tetramide is a neutral molecule, it was not eluted into DMSO. One way to overcome this obstacle is to eliminate the diamine pillars. This was accomplished by treating the diamine-pillared clay-macrocycle structure with a concentrated solution of LiCl in DMSO. In this treatment, the Li^+ ions replace the diamine pillars and the macrocycle is simulteneusly liberated into the DMSO solution. The addition of acetone precipitates a mixture of the diamine dihydrochloride salt and the tetraamido macrocycle. The diamine salt is converted into the water-soluble neutral form by treatment with a dilute solution of Na_2CO_3 to leave behind the tetramide as a pure solid in good yield (60%). The isolation of the pure cyclic tetramide enables its direct identification by ^1H NMR spectroscopy and mass spectrometry. Indeed, the ^1H NMR spectrum is identical to that reported in the literature,[6a] whereas the mass spectrum shows clearly the molecular ion peak at m/z 532 (see the Supporting Information).

Experimental Section

The clay was a natural Wyoming sodium montmorillonite SWy-1 obtained from the Source Clay Minerals Repository at the University of Missuri, Columbia. It was purified by well-established procedures in clay science. The cationic-exchange capacity (cec) is 80 mequiv per 100 g clay. To prepare the pillared-clay a solution of the *p*-xylylenediamine dihydrochloride salt (125 mg) in water (0.6 mmol, 1.5 × cec) was added to a stirred clay suspension of Na^+-MNT (1 g) in water (20 mL). The mixture was stirred for 1 h, centrifuged, washed with water three times, and air-dried. The dry powder was dispersed in water (30 mL) and a solution of *p*-xylylenediamine (110 mg, 0.8 mmol, 2 × CEC) in water (40 mL) was added. The mixture was stirred for 1 h, and the product was collected by centrifugation and, without washing, was air-dried. A CH_3CN solution (30 mL) containing the isophthaloyl dichloride (490 mg, 2.4 mmol) and Et_3N (242 mg, 2.4 mmol) was added to the dry powder in CH_3CN (30 mL) and the mixture stirred for 24 h. The product was collected by centrifugation and washed with CH_3CN (30 mL). The clay complex was dispersed in LiCl-DMSO solution (20 mL) to remove the organic impurities from the clay. Acetone (50 mL) was added to the organic phase to precipitate the amide tetramer and the *p*-xylylenediamine dihydrochloride salt. The mixture was treated with a diluted Na_2CO_3 solution to convert the diamine salt into the water soluble neutral diamine, thus leaving the tetramide as a pure solid (130 mg, 60% yield). ^1H NMR (300 MHz, $[D_6]$DMSO): $\delta = 4.4$ (s, 8H, CH_2), 7.34 (s, 8H, *p*-xylyl H), 7.56 (t, 2H, isophthaloyl 5-H), 7.9 (d, 4H, isophthaloyl 4-H and 6-H), 8,32 (s, 2H, isophthaloyl 2-H), 9,0 (t, 4H, CONH); FT-IR (KBr): $\tilde{\nu}$: 1635, 1530 cm^{-1} (CONH); EI-MS: m/z: 532 $[M^+]$.

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