

brought about by reaction with the epoxide center. Such a hypothesis would be consistent with earlier observations that simple azinomycin analogues based upon just the “left-hand” domain of the azinomycins are highly cytotoxic.^[12, 18] Additionally, it is notable that the synthetic agents **5**, and **6** retained activity in the two cell lines possessing acquired resistance to the widely used drug cisplatin, which forms a variety of intrastrand and interstrand bifunctional crosslinks on DNA.

In summary, our results suggest that synthetic azinomycin analogues such as **5** can be readily assembled, and induce ISC in double-stranded DNA along similar lines to the natural products. In view of the limited availability of the azinomycins, we believe that these and other analogues will prove useful in further addressing the molecular mechanism of action of this class of antitumor agent.

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- [10] HPLC retention times (Chiralpak AD column): (*E*)-**8** (98% *ee*, 5% isopropyl alcohol (IPA)/hexanes, 1.0 mL min⁻¹) = 14.27 min (*S*), 13.43 min (*R*); **10** (18% IPA/hexanes, 1.0 mL min⁻¹): *E* isomer (90% *ee*) = 8.35 min (*S*), 10.98 min (*R*); *Z* isomer (89% *ee*) = 7.74 min (*S*), 7.34 min (*R*). Racemic materials were prepared and used for comparison purposes.
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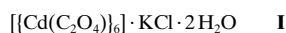
Fascinating Alkali Halide Structures of Different Dimensionalities Incorporated in Host Lattices

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Design and synthesis of supramolecular inorganic structures exhibiting novel host–guest interactions and molecular recognition have provided exciting new possibilities.^[1, 2] Some of these materials contain cages for ions or cation–anion aggregates, polyoxometalates with cages containing ions such as Cl⁻ and NO₃⁻, and ion-pairs such as NH₄⁺Cl⁻, being good examples.^[3] Several classes of inorganic–organic hybrid materials wherein the organic molecules subtly determine the structures of metal oxide lattices have also been prepared in recent years.^[4] Amongst these, metal–organic networks described in the recent literature^[5–7] are noteworthy, besides the large variety of inorganic open-framework structures, such as the metal phosphates^[8] and oxalates^[9] synthesized hydrothermally in the presence of organic amines. However, there is no report of materials to date, wherein extended structures of ionic compounds are incorporated in host lattices. Herein we report for the first time novel oxalate materials containing alkali halides with entirely new structures. The structures described include, a three-dimensional expanded KCl, a two-dimensional layered RbCl, and a one-dimensional KBr chain. The study makes an important addition to the chemistry of inorganic host–guest materials and suggests that many more such structures can indeed be synthesized.

To prepare materials incorporating new alkali halide structures, we have employed the hydrothermal method of synthesis, which is known to yield materials not obtained ordinarily.^[4, 10] The basic reaction employed is the simple exchange reaction between a cadmium halide and an alkali metal oxalate, carried out in the presence of an amine. The three new Cd oxalates containing alkali halides obtained by this means have the compositions **I–III**.

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The structure of **I** (Figure 1 a) contains some extraordinary features.^[11] First, it has a cadmium oxide cluster of the composition $[\text{Cd}_6\text{O}_{24}]$, containing Cl^- ions in the center and

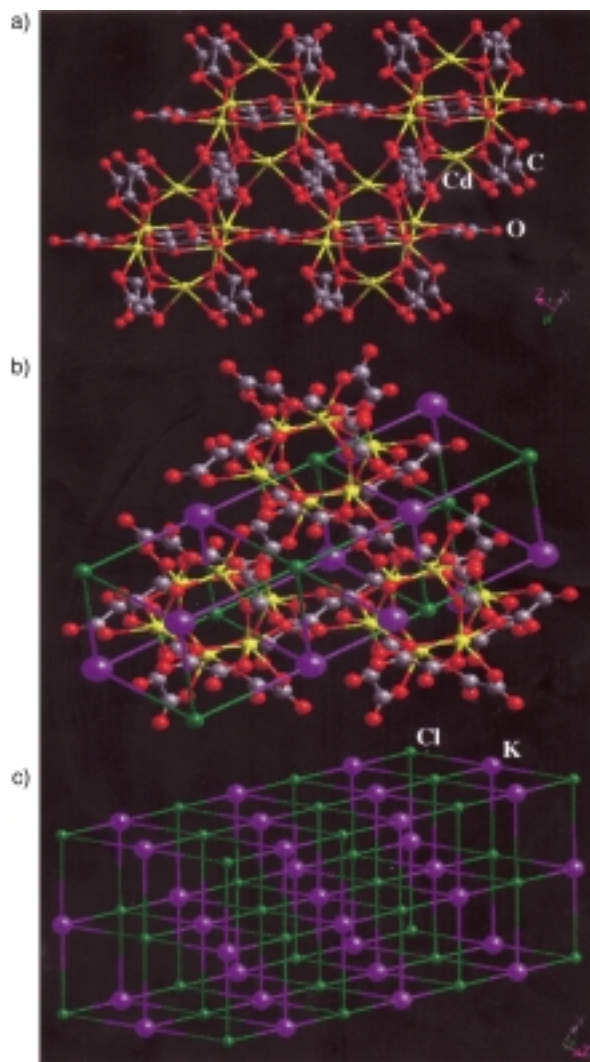


Figure 1. a) The structure of $[\text{Cd}(\text{C}_2\text{O}_4)_6] \cdot \text{KCl} \cdot 2\text{H}_2\text{O}$ (**I**) without the KCl guest. b) Structure of **I**, showing the host and the guest species, along the [001] direction. The KCl lattice can also be visualized. c) Expanded cubic structure of KCl. Note that the [100] KCl is along the [111] direction of the cadmium oxalate **I**.

with Cd in triangular prismatic coordination (Figure 1 b). To our knowledge, this is the first example of such Cd–O clusters. The $[\text{Cd}_6\text{O}_{24}]$ clusters are connected to each other through the oxalate units. Charge compensation for the Cl^- ions in the cluster is provided by the K^+ ions, located outside the clusters (Figure 1 b). Remarkably, the relative positions of the K^+ and Cl^- ions are perfectly ordered in three-dimensions forming an independent rock-salt structure with interpenetrating

FCC lattices (Figure 1 c). The cubic unit cell parameter of KCl is 13.4 Å, which is double that of ordinary KCl (6.7 Å). The [100] KCl planes run along the [111] direction of **I**. The K^+ ions are coordinated by 12 oxygen atoms at a distance of ~ 3 Å, and the Cl^- ions are coordinated by six cadmium ions at ~ 2.9 Å. We consider the incorporation of the KCl structure with an expanded unit cell in a host matrix to be noteworthy. An alternate way to describe the structure of **I** would be as follows: The Cl^- ion is at the center of a cluster of six Cd trigonal prisms, arranged in such a manner that the nearest neighbors are six Cd ions at the vertices of an octahedron, the next nearest neighbors being oxygen atoms of the six trigonal prisms, reminiscent of Chevrel phases. Thus, we could consider **I** as a rock salt arrangement of the two clusters, $[\text{ClCd}_6(\text{C}_2\text{O}_4)_3]^{5+}$ and $[\text{K}(\text{H}_2\text{O})_2(\text{C}_2\text{O}_4)_3]^{5-}$. This is indeed an illustration of “scale chemistry”, of the type proposed recently by Férey.^[12]

Encouraged by the above finding, we attempted to synthesize the rubidium halide analogue by carrying out the reaction of a 2:1 mixture of RbCO_3 and oxalic acid with other reactants. We, however, obtained a product with the composition **II**, with an entirely different structure.^[11b, 13] Compound **II** has a layer oxalate structure (Figure 2), with two closely spaced hexagonal RbCl layers separated by 3.3 Å. The RbCl layers are made of hexagonal Rb_3Cl_3 units (see inset of Figure 2) with an average Rb–Cl distance of ~ 3.6 Å (compared to 3.3 Å in solid RbCl of rock-salt structure). The hexagon has the chair conformation of cyclohexane. The RbCl layers are stabilized by the oxalate layer, present after every two RbCl layers, by providing the additional coordination required by the Rb^+ and Cl^- ions. The Cd ions are coordinated by four oxygen atoms at an average distance of 2.29 Å and by two chlorine atoms at 2.57 Å.

By the reaction of CdBr_2 with $\text{K}_2\text{C}_2\text{O}_4$, we have obtained a material of the composition **III**.^[11b, 14] Compound **III** is a three-dimensional Cd oxalate, with oxalate layers similar to that in **II**, but linked by oxalate bridges.^[9] This is also evident from the lattice parameters of **II** and **III**. One of the lattice parameters of **III** is ~ 5 Å larger than that in **II**, indicating that the *out-of plane* oxalate bridges the cadmium oxalate layers along that axis to form channels. Accordingly, one of the axes differs significantly in **II** compared to **III**. The K^+ ions located in the channels of **III** form linear KBr chains (Figure 3), with K–Br distances in the range 3.36–3.50 Å. The interchain Br–Br distance is 3.76 Å and the K^+ ions are coordinated by the oxalate oxygen atoms and the Br atoms.

The expanded KCl, the layered RbCl , and KBr chain reported here are most unusual in the sense that such structures were hitherto unknown. It has been possible to form these structures because of host–guest interactions, the host providing the additional coordination necessary to stabilize the structures. The guest species, involving extended ionic lattices, reported here are distinctly different from those resulting from ion-exchange in layered solids, such as the metal–anion arrays in oxide hosts,^[15] and somewhat comparable to the KCl/CsCl lattice in a phosphate framework obtained in a molten salt medium.^[16]

The present study demonstrates that it should be possible to isolate many more such materials containing extended alkali

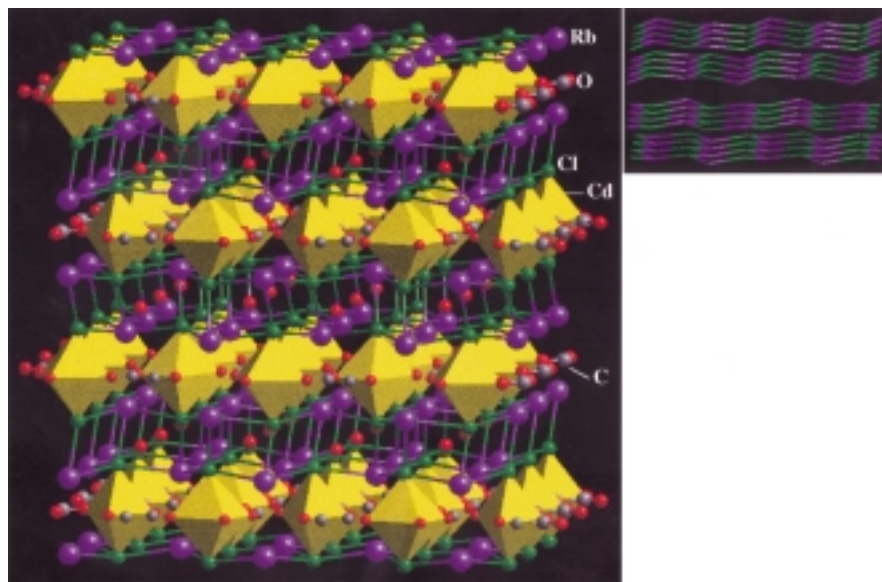


Figure 2. Structure of $[\text{Cd}(\text{C}_2\text{O}_4)] \cdot 2\text{RbCl} \cdot \text{H}_2\text{O}$ (**II**), showing the $\text{Cd}(\text{C}_2\text{O}_4)_2\text{Cl}_2$ layers with CdO_4Cl_2 octahedra (in yellow) along the $[100]$ direction. Layered RbCl can be seen in between the Cd oxalate layers. Note that the Cl^- ions are bonded to the Cd center and point into the interlamellar space. Inset: Arrangement of RbCl layers.

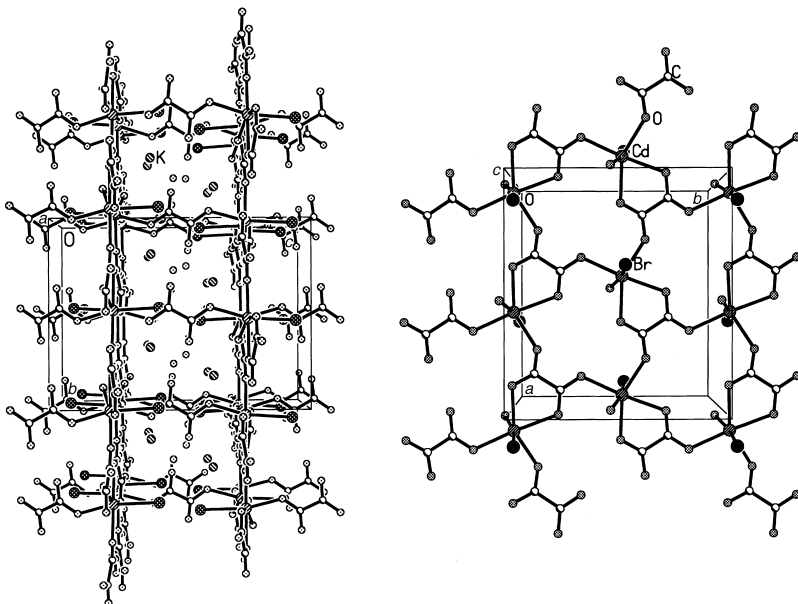
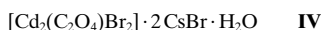


Figure 3. Left) Structure of $[\text{K}_2\text{Cd}_2(\text{C}_2\text{O}_4)_3] \cdot 2\text{KBr} \cdot 2\text{H}_2\text{O}$ (**III**) along the $[100]$ direction. Note that the oxalate group connects the two layers. K and water molecules are situated inside the channels. One-dimensional KBr chains can be seen. Right) Structure of the layer in **III**.

halide structures. In fact, we have just isolated a new compound of the formula **IV**, in which CsBr has a layer structure. It appears that the lower dimensional alkali halide structures are favored by larger alkali and halide ions as well as by a low oxalate:alkali halide ratio.



Experimental Section

I: $\text{K}_2\text{C}_2\text{O}_4$ (0.229 g) was added to a butan-2-ol/water mixture (2.3 mL, 0.6 mL) and stirred for 20 min. CdCl_2 (0.25 g) and glacial acetic acid

(0.28 g) were added to this solution under constant stirring. Finally, imidazole (0.127 g) was added and the mixture was homogenized for 2 h. The reaction mixture with the composition $\text{CdCl}_2:\text{K}_2\text{C}_2\text{O}_4:\text{CH}_3\text{COOH}:\text{C}_4\text{H}_9\text{OH}:\text{H}_2\text{O}$: 100(4):100(1):100(1):100(1) was sealed in a PTFE-lined stainless-steel autoclave and heated at 165°C for 55 h. The product containing crystals of **I** with a rodlike morphology was filtered, washed with deionized water, and dried under ambient conditions.

II: Rb_2CO_3 (0.287 g) and $\text{H}_2\text{C}_2\text{O}_4$ (0.157 g) were added to a butan-2-ol/water mixture (2.3 mL, 0.6 mL) and stirred for 20 min. CdCl_2 (0.25 g) and CH_3COOH (0.28 g) were added to this solution under constant stirring. Finally, imidazole (0.128 g) was added and the mixture was homogenized for 90 min. The gel was sealed in a PTFE-lined stainless-steel Parr autoclave and heated at 165°C for 55 h. Platelike crystals of **II** which resulted from this reaction were filtered, washed with deionized water, and dried under ambient conditions.

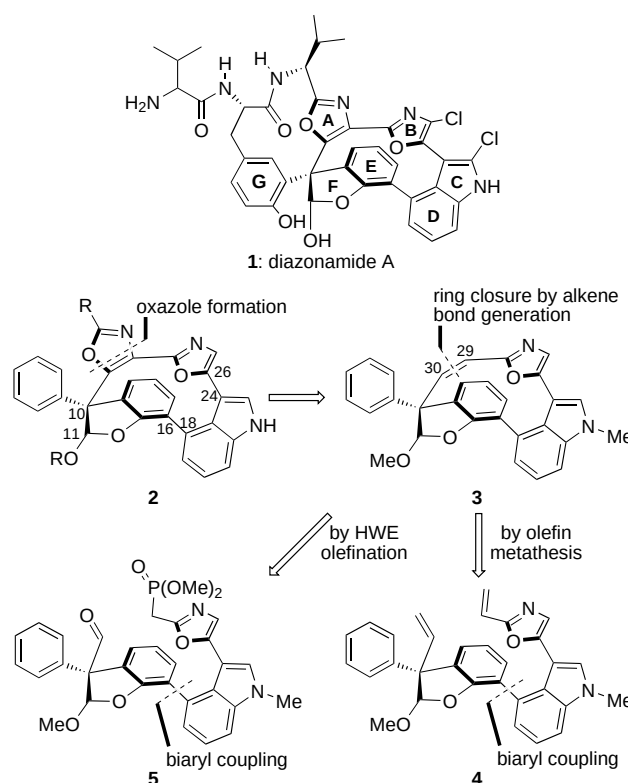
III: K_2CO_3 (0.102 g) and $\text{H}_2\text{C}_2\text{O}_4$ (0.125 g) were added to a butan-2-ol-water mixture (1.8 mL, 0.5 mL) and stirred for 5 min. CdBr_2 (0.2 g) and CH_3COOH (0.11 g) was added under constant stirring and the mixture was homogenized for 90 min. The gel with a composition $\text{CdBr}_2:\text{K}_2\text{CO}_3:1.35\text{H}_2\text{C}_2\text{O}_4:2.5\text{CH}_3\text{COOH}:27\text{C}_4\text{H}_9\text{OH}:38\text{H}_2\text{O}$ was sealed in a PTFE-lined stainless-steel Parr autoclave and heated at 150°C for 80 h. Rodlike crystals of **III** which resulted from this reaction were filtered, washed with deionized water, and dried under ambient conditions.

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diffractometer. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-145227 (**I**), CCDC-145228 (**II**), and CCDC-145229 (**III**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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- [14] Crystal data for **III**: $\text{K}_2\text{Cd}(\text{C}_2\text{O}_4)_3 \cdot 2\text{KBr} \cdot 2\text{H}_2\text{O}$, $M_r = 841.12$, crystal dimensions $0.12 \times 0.12 \times 0.24\text{ mm}$, orthorhombic, space group, *Pbca*, $a = 11.898(6)$, $b = 10.963(1)$, $c = 15.203(6)\text{ Å}$, $V = 1983.2(2)\text{ Å}^3$, $Z = 4$, $\rho_{\text{calcd}} = 2.817\text{ g cm}^{-3}$, $\mu(\text{Mo K}\alpha) = 7.077\text{ mm}^{-1}$, $\lambda = 0.71073\text{ Å}$. The structure was solved by direct methods (SHELXTL-PLUS), 7521 reflections, 1428 independent reflections. Full-matrix least-squares on $|F^2|$ (SHELXS-93, G. M. Sheldrick, Gottingen, **1993**) to $R_1 = 0.03$ and $wR_2 = 0.05$. Residual density, min./max.: $-0.593/0.369\text{ e Å}^{-3}$.^[11b]
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Scheme 1. Structure of diazonamide A (**1**) and retrosynthetic analysis of model system **2**.

Model Studies towards Diazonamide A: Synthesis of the Heterocyclic Core**

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Diazonamide A (**1**, Scheme 1), a secondary metabolite isolated from the colonial ascidian *Diazona chinensis*, exemplifies an unprecedented molecular architecture encompassing a cyclic polypeptide backbone as well as an admirably

complex and strained halogenated heterocyclic core trapped as a single atropisomer harboring a quaternary center at the epicenter.^[1] Beyond the formidable synthetic challenge posed by such a daunting molecular framework, diazonamide A possesses potent in vitro cytotoxicity against human colon carcinoma and B-16 murine melanoma cell lines with IC_{50} values in the nanomolar range. These biological actions, however, are exerted through an unknown mode of action. Unfortunately, more extensive bioassays have been hampered by an inability to harvest additional material from the original source. As such, diazonamide A represents one of the most enticing natural products isolated in recent years and a serious challenge to synthetic chemists. Although several groups have reported progress on particular structural subunits of diazonamide A,^[2] no one has yet successfully prepared the fully unsaturated 12-membered polycycle. Herein we report the first synthesis of this heteroaromatic macrocyclic core by a concise and novel strategy which proceeds to provide atropisomerically pure product.

Since we envisioned from the outset that the heterocyclic core would pose the greatest synthetic challenge for a total synthesis of diazonamide A, we focused our efforts primarily on the preparation of model system **3** (Scheme 1) as a means to address key synthetic issues such as potential atropisomerism along the $\text{C}_{16}-\text{C}_{18}$ and $\text{C}_{24}-\text{C}_{26}$ biaryl linkages. As shown in Scheme 1, our synthetic rationale was based on two fairly obvious but strategic bond disconnections. Because numerous methods are currently available to generate macrocycles by alkene bond formation, we felt that disconnection of the $\text{C}_{29}-\text{C}_{30}$ alkene would be prudent and could potentially arise in the

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