0.33 mmol). After the mixture had been stirred for 30 min at room temperature, ferrocene **3** (12 mg, 0.025 mmol) was added, and the resulting solution was then cooled to 10 °C. Stirring was continued for an additional 10 min at this temperature, and the aldehyde (0.25 mmol) was then added directly in one portion. The Schlenk flask was sealed, and the reaction mixture was stirred at 10 °C overnight. Quenching with water followed by extracting with dichloromethane, drying of the combined organic phase over $MgSO_4$, and evaporating the solvent under reduced pressure gave the crude product. Column chromatography (silica gel; eluents: hexanes/diethyl ether) afforded the pure secondary alcohol (for *ee* analyses by HPLC see Supporting Information).

Received: May 29, 2000 [Z 15183]

---

[1] For examples see: a) K. Meguro, M. Aizawa, T. Sohda, Y. Kawamatsu, A. Nagaoka, *Chem. Pharm. Bull.* **1985**, *33*, 3787; b) F. Toda, K. Tanaka, K. Koshiro, *Tetrahedron: Asymmetry* **1991**, *2*, 873; c) M. Botta, V. Summa, F. Corelli, G. Di Pietro, P. Lombardi, *Tetrahedron: Asymmetry* **1996**, *7*, 1263; d) S. Stanchev, R. Rakovska, N. Berova, G. Snatzke, *Tetrahedron: Asymmetry* **1995**, *6*, 183.

[2] a) E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1995**, *36*, 9153; b) E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1996**, *37*, 4837; c) E. J. Corey, C. J. Helal, *Tetrahedron Lett.* **1996**, *37*, 5675; d) general review: E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986.

[3] a) T. Ohkuma, M. Koizumi, H. Ikehira, T. Yokozawa, R. Noyori, *Org. Lett.* **2000**, *2*, 659; b) general review: R. Noyori, T. Ohkuma, *Pure Appl. Chem.* **1999**, *71*, 1493.

[4] For catalyses of this type involving metals other than zinc, see: a) Ti: B. Weber, D. Seebach, *Tetrahedron* **1994**, *50*, 7473; b) Rh/B: M. Sakai, M. Ueda, N. Miyaura, *Angew. Chem.* **1998**, *110*, 3475; *Angew. Chem. Int. Ed.* **1998**, *37*, 3475. For early studies of enantioselective versions involving stoichiometric amounts or excess of organometallic reagents, see: c) D. Seebach, A. K. Beck, S. Roggo, A. Wonnacott, *Chem. Ber.* **1985**, *118*, 3673; d) R. Noyori, S. Suga, K. Kawai, S. Okada, M. Kitamura, *Pure Appl. Chem.* **1988**, *60*, 1597; e) K. Tomioka, M. Nakajima, K. Koga, *Chem. Lett.* **1987**, 65; f) M. Kaino, K. Ishihara, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3736; g) J.-T. Wang, X. Fan, X. Feng, Y.-M. Qian, *Synthesis* **1989**, 291; h) M. Nakajima, K. Tomioka, K. Koga, *Tetrahedron* **1993**, *49*, 9751.

[5] Reviews on diorganozinc additions to aldehydes: a) R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, *103*, 34; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49; b) K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833; c) K. Soai, T. Shibata in *Comprehensive Asymmetric Catalysis, Vol. 2* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, p. 911.

[6] a) K. Soai, Y. Kawase, A. Oshio, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1613; b) for a diastereoselective version, see: J. Hübscher, R. Barner, *Helv. Chim. Acta* **1990**, *73*, 1068.

[7] a) P. I. Dosa, J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1997**, *62*, 444; b) for a 3-*exo*-(dimethylamino)isoborneol (DAIB)-catalyzed asymmetric addition of $ZnPh_2$ to ketones, see: P. I. Dosa, G. C. Fu, *J. Am. Chem. Soc.* **1998**, *120*, 445.

[8] a) W.-S. Huang, L. Pu, *J. Org. Chem.* **1999**, *64*, 4222; b) W.-S. Huang, Q.-S. Hu, L. Pu, *J. Org. Chem.* **1999**, *64*, 7940; c) W.-S. Huang, L. Pu, *Tetrahedron Lett.* **2000**, *41*, 145.

[9] C. Bolm, K. Muñiz, *Chem. Commun.* **1999**, 1295.

[10] For the use of ferrocene **3** in dialkylzinc additions, see: a) C. Bolm, K. Muñiz-Fernández, A. Seger, G. Raabe, *Synlett* **1997**, 1051; b) C. Bolm, K. Muñiz Fernández, A. Seger, G. Raabe, K. Günther, *J. Org. Chem.* **1998**, *63*, 7860; c) C. Bolm, K. Muñiz, J. P. Hildebrand, *Org. Lett.* **1999**, *1*, 491.

[11] For selected reports on other mixed zinc species, see: a) H. Nehl, W. R. Scheidt, *J. Organomet. Chem.* **1985**, *289*, 1; b) W. Oppolzer, R. N. Radinov, *Helv. Chim. Acta* **1992**, *75*, 170; c) S. Berger, F. Langer, C. Lutz, P. Knochel, T. A. Mobley, C. K. Reddy, *Angew. Chem.* **1997**, *109*, 1603; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1454; d) C. Lutz, P. Knochel, *J. Org. Chem.* **1997**, *62*, 7895; e) P. Wipf, S. Ribe, *J. Org. Chem.* **1998**, *63*, 6454; f) L. Tan, C. y. Chen, R. D. Tillyer, E. J. J. Grabowski, P. J. Reider, *Angew. Chem.* **1999**, *111*, 724; *Angew. Chem. Int. Ed.* **1999**, *38*, 711.

[12] An example of the use of a combination of $ZnPh_2$ and $ZnMe_2$ in this reaction has been described before: Phenyl transfer to nicotinaldehyde catalyzed by *N,N*-diethylnorephedrine resulted in phenyl transfer with 20:1 selectivity to give 3-phenylpyridylmethanol in 70 % *ee*, while the addition of $ZnPh_2$ only afforded the product alcohol in 73 % *ee*; J. Blacker in *Third International Conference on the Scale Up of Chemical Processes* (Conference Proceedings) (Ed.: T. Laird), Scientific Update, UK, **1998**, p. 74.

[13] In this study only isolated diphenylzinc (purchased from Strem) was used. For the preparation of other salt-free diarylzinc compounds and their subsequent catalyzed asymmetric addition to aldehydes, see: A. J. Blacker, J. M. Fielden (Zeneca), WO 98/28306, **1998**.

[14] We presume that ethylphenylzinc is formed in an equilibrium with diethylzinc and diphenylzinc. Apparently, the ethyl group then behaves as a nontransferable moiety on zinc, while phenyl is transferred to the aldehyde with complete selectivity (no ethyl addition product was found). In order to reveal the nature of the zinc species, we used low-temperature ^1H NMR techniques. In a mixture of $ZnEt_2$ and $ZnPh_2$ (2:1 ratio) in $[D_8]$toluene only one set of ethyl group signals was observed at almost the same position as the ones of $ZnEt_2$ ($\Delta\delta(CH_2) = 0.03$ ppm). In $[D_8]$THF at $-80\,^{\circ}C$ additional sets of ethyl and phenyl group protons were detected belonging to a new, albeit not yet identified species. Further studies are in progress to characterize the most relevant intermediates in this catalysis.

[15] a) C. van der Stelt, W. J. Heus, W. T. Nauta, *Arzneim. Forsch.* **1969**, *19*, 2010; b) R. F. Rekker, H. Timmerman, A. F. Harms, W. T. Nauta, *Arzneim. Forsch.* **1971**, *21*, 688; c) A. F. Casy, A. F. Drake, C. R. Ganellin, A. D. Mercer, C. Upton, *Chirality* **1992**, *4*, 356.

A Synthetic Azinomycin Analogue with Demonstrated DNA Cross-Linking Activity: Insights into the Mechanism of Action of this Class of Antitumor Agent[**]

John A. Hartley,* Ali Hazrati, Lloyd R. Kelland,*
Ruzwana Khanim, Michael Shipman,* Franck Suzenet,
and Louise F. Walker

Chemical agents capable of inducing DNA interstrand cross-links (ISCs) comprise an extremely important class of clinical cancer chemotherapeutic agents.[2] The azinomycins (**1**

---

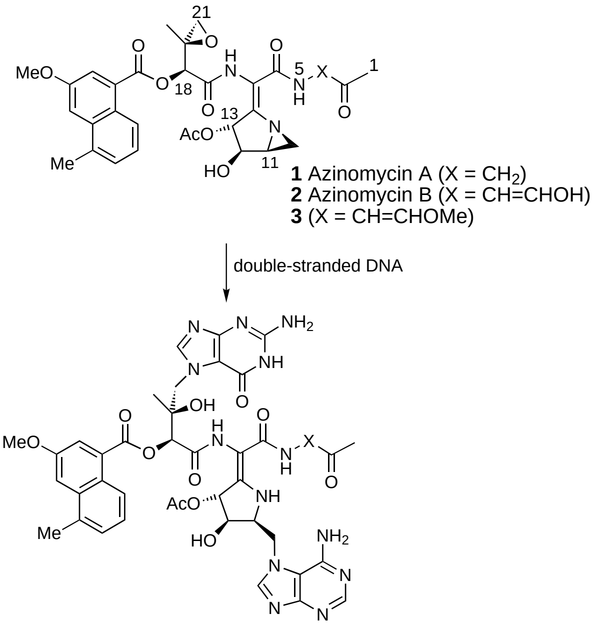
[*] Prof. J. A. Hartley, A. Hazrati, R. Khanim
CRC Drug-DNA Interactions Research Group
Department of Oncology
Royal Free & University College Medical School
University College London
91 Riding House Street, London W1P 8BT (UK)
Fax: (+44) 20-7436-2956
E-mail: john.hartley@ucl.ac.uk

Dr. L. R. Kelland
CRC Centre for Cancer Therapeutics
Institute of Cancer Research
Sutton, Surrey, SM2 2NG (UK)
Fax: (+44) 181-7224101
E-mail: lloyd@icr.ac.uk

Dr. M. Shipman, Dr. F. Suzenet, Dr. L. F. Walker
School of Chemistry
University of Exeter
Stocker Road, Exeter, EX4 4QD (UK)
Fax: (+44) 1392-263434
E-mail: m.shipman@exeter.ac.uk

[**] The authors gratefully acknowledge the financial support provided by the CRC and the EPSRC. We are indebted to the EPSRC National Mass Spectrometry Centre for performing mass spectral measurements, and the EPSRC Chemical Database Service at Daresbury.[1]

and **2**, Scheme 1) are a unique class of antibiotic which possess potent in vitro cytotoxic activity, significant in vivo antitumor activity, and which appear to act by ISC formation.[3] Two reports have been published which provide insights into how these natural products induce ISCs in double-stranded DNA. By using synthetic oligonucleotide duplexes, Armstrong et al. demonstrated that azinomycin B causes ISCs in the major groove of DNA by alkylation at N-7 of guanine (G) and reaction with another purine residue (A or G) two bases along on the complementary DNA strand.[4] Recently, Fujiwara et al. isolated and partially characterized adduct **4**, produced upon treatment of the 4-methyl azinomycin B derivative **3** with the self-complementary oligodeoxynucleotide [d(TAGCTA)$_2$], work which provided the first direct evidence of the involvement of the electrophilic epoxide and aziridine moieties in the DNA cross-linking event (Scheme 1).[5]

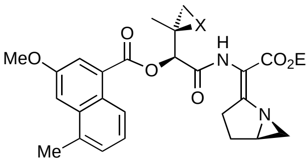


1 Azinomycin A (X = CH$_2$)
2 Azinomycin B (X = CH=CHOH)
3 (X = CH=CHOMe)

4 (X = CH=CHOMe)

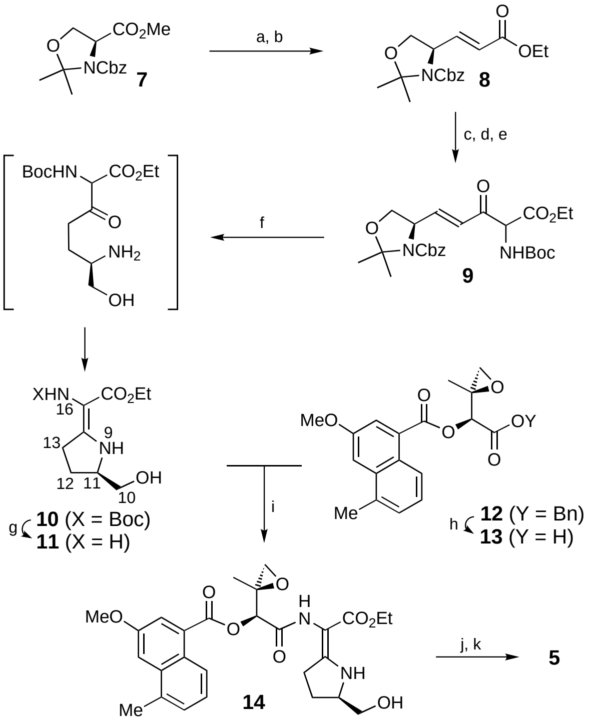
Scheme 1. Mechanism of action of the azinomycins, the azinomycins bind to two purine residues.

To fully elucidate the mechanism of action of the azinomycins, work which might ultimately lead to the development of new clinically useful ISC agents, further studies are needed to determine the timing of the alkylation events that lead to ISC formation and to ascertain the role of other functional groups within the azinomycins (e.g. naphthyl residue, C-12/C-13 hydroxy groups) in DNA sequence recognition. One powerful way to address these issues would be to make simplified yet mechanistically fully functional analogues of the natural products. Surprisingly, despite the large volume of work that has been directed towards realizing the first total synthesis of the azinomycins,[6] no reports have appeared on the ISC activity of any synthetic azinomycin derivatives. Herein we describe a flexible and efficient approach for the assembly of the basic C-6 to C-21 carbon skeleton of the azinomycins and demonstrate that this approach can be used to prepare simplified azinomycin analogues such as epoxy aziridine **5** and cyclopropyl aziridine **6**. Furthermore the analogue **5** is an ISC agent and acts by a similar mechanism to that of the natural products.



5 (X = O)
6 (X = CH$_2$)

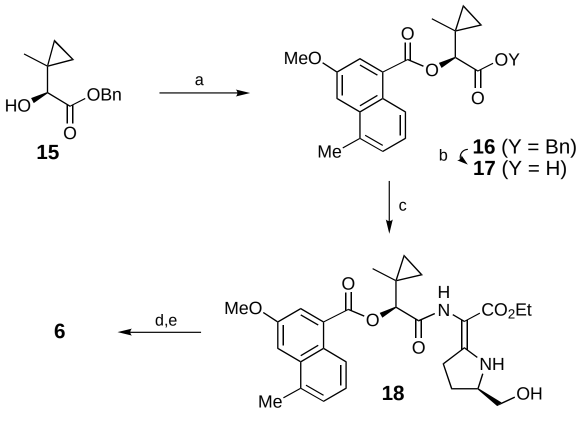
Our synthesis of epoxy aziridine **5** is depicted in Scheme 2. Homochiral ester **7**,[7] readily obtained from L-serine in three steps, was transformed into α,β-unsaturated ester **8** by DIBAL reduction and subsequent olefination by using (carboethoxymethylene)triphenylphosphorane. Further homologation of ethyl ester **8** to α-amino-β-ketoester **9** was accomplished by conversion to the acid chloride and coupling with EtO$_2$CCH(CO$_2$H)(NHBoc) in the presence of magnesium ethoxide.[8] Then, a pivotal step in the synthesis was executed by the hydrogenation of **9** in EtOH in the presence of aqueous hydrochloric acid to give dehydroamino acid **10** in 68 % yield. We suggest that these reaction conditions produce the γ-amino ketone which undergoes spontaneous cyclization to the corresponding cyclic imine which then tautomerizes to the



Scheme 2. Synthesis of the azinomycin analogue **5**. a) DIBAL, toluene, −78 °C, 95 %; b) Ph$_3$P=CHCO$_2$Et, toluene, 77 %; c) NaOH, THF, H$_2$O; d) (COCl)$_2$, DMF (catalyst), CH$_2$Cl$_2$; e) EtO$_2$CCH(CO$_2$H)(NHBoc), Mg(OEt)$_2$, CCl$_4$, 54 % from **8**; f) H$_2$, Pd/C, EtOH, HCl(aq), 68 %; g) TFA, CH$_2$Cl$_2$; h) H$_2$, Pd/C, MeOH; i) PyBOP, HOBt, Et$_3$N, DMF, 67 % from **12**; j) MsCl, Et$_3$N, −78 °C, CH$_2$Cl$_2$, 91 %; k) TBAF, 4 Å sieves, THF, 15 min, TLC, 45 %. PyBOP = benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, HOBt = 1-hydroxy-1*H*-benzotriazole, TBAF = tetrabutylammonium fluoride, MsCl = methanesulfonyl chloride, TFA = trifluoroacetic acid, Boc = *tert*-butoxycarbonyl, DIBAL = diisobutylaluminum hydride.

thermodynamically more stable **10**. Dehydroamino acid **10** is produced as a variable mixture of geometric isomers in favor of the desired *E* isomer (*E*:*Z*; 10:1 to 6:1 (in $CDCl_3$)) as determined by NOE measurements,[9] and in reproducibly high enantiomeric excess (*E* isomer = 90% *ee*; *Z* isomer = 89% *ee*) as established by chiral HPLC analysis.[10] As yet, we have been unable to ascertain the source of the small amount of racemization observed in the conversion of **8** into **10**. Coupling of carboxylic acid **13**, produced by hydrogenation of benzyl ester **12**,[6b] with 1.5 equivalents of amine **11** (formed by removal of the *N*-Boc group from **10**) yielded **14** in 67% yield, as a mixture of geometric isomers (9:1 (in $CDCl_3$)). Finally, ring closure to give 1-azabicyclo[3.1.0]hexane **5** was accomplished via the corresponding mesylate according to methodology originally devised by Terashima and co-workers.[11] In our hands, this ring closure was best performed with TBAF[6c] which provides the bicyclic compound **5** in 45% yield after rapid preparative thin-layer chromatography (TLC) on plates pretreated with triethylamine.

To study the mechanism of DNA cross-link formation by using simplified azinomycin analogues, we have also prepared **6**, containing a "left-hand" domain in which the electrophilic epoxide moiety has been replaced by the chemically inert cyclopropane ring. This was achieved by esterification of homochiral alcohol **15**[12] with 5-methyl-3-methoxy-1-naphthoyl chloride to give benzyl ester **16** (Scheme 3). Subsequent hydrogenolysis of this ester gave the corresponding acid **17**, which was coupled with amine **11** and further converted into **6** via **18** as described above for **5**. Whilst the gross struture of the bicyclic compounds **5** and **6** have been established unambiguously, the stereochemical assignment about the tetrasubstituted double bond can only be tentatively assigned as *trans*, based on comparisons with the earlier synthetic intermediates (e.g. **10**, Scheme 2).[13]



Scheme 3. Synthesis of the azinomycin analogue **6**. a) 5-Methyl-3-methoxy-1-naphthoyl chloride, DMAP (catalyst), Et_3N, CH_2Cl_2, 85%; b) H_2, Pd/C, MeOH; c) PyBOP, HOBt, Et_3N, DMF, **11**, 65% from **16**; d) MsCl, Et_3N, −78°C, CH_2Cl_2, 80%; e) TBAF, 4 Å molecular sieves, THF, 15 min, TLC, 34%. DMAP = 4-dimethylaminopyridine

By using an agarose gel assay,[14] we have studied the interstrand cross-linking activity of three of our synthetic azinomycin compounds (**5**, **6**, **14**). We have determined that epoxy aziridine **5** produces DNA cross-links (100% cross-link formation at 100 μM after 1.5 h), whereas **6** and **14**, devoid of the epoxide or the aziridine, respectively, show little more than background-level activity (Figure 1). Thus, the presence of both functional groups is essential for ISC formation and indicates that **5** is acting on DNA in a similar manner to the natural products (see above). In an effort to elucidate the sequence specificity of these agents, we have evaluated them in a Taq DNA polymerase stop assay.[15] All three analogues (**5**, **6**, **14**) induce Taq stops preferentially at G residues indicating alkylation at these bases, an observation which lends further credence to the idea that these compounds mimic the azinomycins (data not shown).[4, 5]

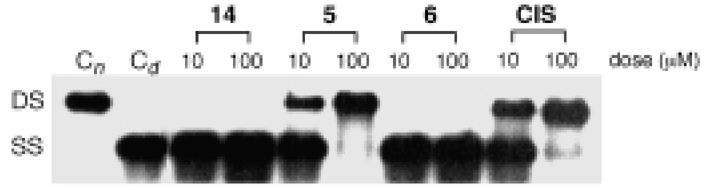


Figure 1. Agarose cross-linking gel for the synthetic azinomycin analogues (**5**, **6**, **14**). Plasmid DNA was treated with the agents at two separate concentrations (10 and 100 μM) for 1.5 h prior to denaturation and gel electrophoresis. CIS is the cross-linking drug cisplatin which was used for comparative purposes. C_n and C_d are control nondenaturated and denatured samples, respectively. DS and SS indicate the positions of double- and single-stranded DNA, respectively.

The cytotoxicity of derivatives (**5**, **6**, **14**) was determined against a small panel of human tumor cell lines (SKOV-3, CH1, A2780 (all ovarian), HT-29 (colon), K-562 (leukemia)) using the SRB[16] or MTT[17] assay (Table 1). Significantly, epoxide **5** displayed markedly greater potency (13–110 times) than the corresponding cyclopropane analogue **6**. Intriguingly, epoxide analogue **14**, devoid of the aziridine ring, showed potency comparable to that of **5**. These observations suggest that the epoxide moiety is largely responsible for the cytotoxic activity of these agents. This could indicate that whilst DNA cross-link formation has been demonstrated for both the azinomycins and the synthetic analogue **5**, in whole cells cytotoxicity may be induced by simple DNA alkylation

Table 1. Cytotoxicity data for **5**, **6**, and **14**.

	IC_{50} [μM][a]		
Human tumor cell lines	**14**	**5**	**6**
A2780	0.06	0.076	5.2
A2780cisR[b]	0.14	0.28	10
CH1	0.058	0.078	8.6
CH1cisR[b]	0.035	0.087	5.8
SKOV-3	0.56	2.1	29
HT29	0.55	0.52	10
K562	0.52	0.143	1.9

[a] Dose of drug inhibiting growth by 50% following a 96 h exposure (1 h in the case of K562) as determined by the SRB assay[16] (MTT assay[17] in the case of K562). [b] Cell line with acquired resistance to cisplatin. SRB = sulforhodamine, MTT = Thiazolyl blue, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.

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 ISCs 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.

Received: June 6, 2000 [Z15232]

---

[1] D. A. Fletcher, R. F. McMeeking, D. Parkin, *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746.

[2] S. R. Rajski, R. M. Williams, *Chem. Rev.* **1998**, *98*, 2723.

[3] a) K. Nagaoka, M. Matsumoto, J. Onoo, K. Yokoi, S. Ishizeki, T. Nakashima, *J. Antibiot.* **1986**, *39*, 1527; b) K. Yokoi, K. Nagaoka, T. Nakashima, *Chem. Pharm. Bull.* **1986**, *34*, 4554; c) S. Ishizeki, M. Ohtsuka, K. Irinoda, K.-I. Kukita, K. Nagaoka, T. Nakashima, *J. Antibiot.* **1987**, *40*, 60.

[4] R. W. Armstrong, M. E. Salvati, M. Nguyen, *J. Am. Chem. Soc.* **1992**, *114*, 3144.

[5] T. Fujiwara, I. Saito, H. Sugiyama, *Tetrahedron Lett.* **1999**, *40*, 315.

[6] a) R. W. Armstrong, J. E. Tellew, E. J. Moran, *Tetrahedron Lett.* **1996**, *37*, 447; b) H. J. Bryant, C. Y. Dardonville, T. J. Hodgkinson, M. B. Hursthouse, K. M. A. Malik, M. Shipman, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1249; c) M. Hashimoto, S. Terashima, *Heterocycles* **1998**, 59; d) R. S. Coleman, J.-S. Kong, T. E. Richardson, *J. Am. Chem. Soc.* **1999**, *121*, 9088; e) Y. Konda, T. Sato, K. Tsushima, M. Dodo, A. Kusunoki, M. Sakayanagi, N. Sato, K. Takeda, Y. Harigaya, *Tetrahedron* **1999**, *55*, 12723, and references therein.

[7] P. L. Beaulieu, P. W. Schiller, *Tetrahedron Lett.* **1988**, *29*, 2019.

[8] These reaction conditions were more effective than published methods (e.g. D. J. Krysan, *Tetrahedron Lett.* **1996**, *37*, 3303).

[9] Selected NOE data for major (*E*)-**10** (simultaneous irradiation of H-13 and H-13′ enhances N-16 (2.0%), H-12 (3.3%), and H-12′ (4.2%); irradiation of N-9 enhances H-11 (6.2%), H-10 (1.5%), and H-10′ (1.0%)).

[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.

[11] Terashima and co-workers have previously reported a synthesis of **5** and demonstrated that it possesses cytotoxic activity (P388 leukemia: IC_{50} 0.0023 μg mL^{-1}); however, no DNA affinity studies were reported by this group, see M. Hashimoto, M. Matsumoto, K. Yamada, S. Terashima, *Tetrahedron Lett.* **1994**, *35*, 2207.

[12] T. J. Hodgkinson, L. R. Kelland, M. Shipman, F. Suzenet, *Biorg. Med. Chem. Lett.* **2000**, *10*, 239.

[13] For bicyclic compounds **5** and **6**, no NOE enhancements on which a stereochemical assignment could be made were observed across the double bond. Significantly, no NOEs were observed across the double bond in the natural products. The double-bond geometry in the natural products was assigned solely on the basis of the surprisingly high chemical shift ($\delta = 10.8$) of the amide hydrogen at N-5 (see ref. [3b]).

[14] J. A. Hartley, M. D. Berardini, R. L. Souhami, *Anal. Biochem.* **1991**, *193*, 131.

[15] M. Ponti, S. M. Forrow, R. L. Souhami, M. D'Incalci, J. A. Hartley, *Nucl. Acid Res.* **1991**, *19*, 2929.

[16] P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Vistica, J. Warren, H. Bokesch, S. Kenney, M. R. Boyd, *J. Nat. Cancer Inst.* **1990**, *82*, 1107.

[17] J. Carmichael, W. G. DeGraff, P. F. Gazdar, J. D. Minna, J. B. Mitchell, *Cancer Res.* **1987**, *47*, 936.

[18] K. S. Gates, H. Zang, *Abstr. Pap. Am. Chem. Soc.* **1999**, *218*, 368.

Fascinating Alkali Halide Structures of Different Dimensionalities Incorporated in Host Lattices

R. Vaidhyanathan, S. Neeraj, P.A. Prasad,
Srinivasan Natarajan, and C.N.R. Rao*

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 NO_3^-, and ion-pairs such as $NH_4^+Cl^-$, 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**.

---

[*] Prof. Dr. C.N.R. Rao, R. Vaidhyanathan, S. Neeraj, P.A. Prasad,
Dr. S. Natarajan
Chemistry and Physics of Materials Unit
and CSIR Centre of Excellence in Chemistry
Jawaharlal Nehru Centre for Advanced Scientific Research
Jakkur P.O., Bangalore 560 064 (India)
Fax: (+91) 80-846-2766
E-mail: cnrrao@jncasr.ac.in