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Synthesis and reactivity of cyclam-based enediynes

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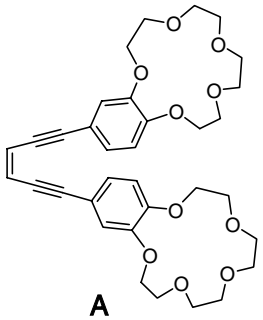
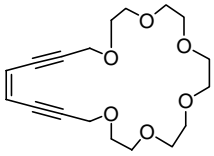
Abstract—Cyclam-based enediynes **1**–**3** have been synthesized for the first time either by direct bis- or tetra-alkylation of the cyclam or via double alkylation of the 1,8-bis-sulfonyl derivative. The enediyne **1** readily forms a complex with Ni(II), which also lowered the onset temperature for Bergman cyclization of the parent enediyne by 60 °C. In the presence of a co-oxidant, MMPP, the Ni-complex can cleave ds-DNA into the nicked relaxed form at micromolar concentrations.

Chemists continue to be fascinated by the enediyne natural products.[1] These are extremely potent cytotoxic agents possesing a unique mechanism of action,[2] that involves their ability to undergo a triggered Bergman cyclization[3] to produce DNA-cleaving diradical species. Harnessing the potent cytotoxicity of these compounds for use in cancer chemotherapy relies upon the ability to design more selective agents.[4] Towards this end, a number of groups have reported the synthesis of novel enediynes with various means of triggering the Bergman cyclization.[5] One approach is to synthesize enediynes in which molecular recognition of metal ions[6] is coupled with a triggering mechanism for the Bergman cyclization. Konig and Rutters[7] and later on Kerwin et al.[8] designed and synthesized the crown ether-based enediynes **A** and **B** (Fig. 1). Although **A** binds both sodium and potassium, neither alkali metal complex of **A** undergoes Bergman cyclization at temperatures lower than that required for cyclization of the free ligand. In contrast to the bis (crown ether) enediyne **A**,[7] in Kerwin's design[8] a crown ether ring **B** was directly incorporated onto the enediyne chromophore, which effectively coupled molecular recognition by the crown to the induction of strain in the enediyne moiety to facilitate the Bergman cyclization. Another macrocyclic system that is also well known for chelation is the azacrown ether. Of particular importance are the cyclams and cyclens both of which have strong coordination ability towards a wide range of cations that include transition metal ions and lanthanides.[9] Their complexes have been widely used as MRI contrast agents,[10] luminescent probes,[11] DNA cleavers, etc.[12] So far, no cyclam/cyclen-based enediyne systems have been developed. A close analogue, namely a tetraaza-macrocycle was reported from this laboratory.[13] In this letter we report the first synthesis of cyclam-based enediynes. The thermal reactivity along with the complexation behaviour of one of the cyclam enediynes is also reported.


A


B

In order to synthesize cyclam-based enediynes, one needs to develop procedures for selective alkylation. Considerable progress has been achieved in this regard. For example, Parker and co-workers[14a] and Wong et al.[14b] developed the synthesis of [1,8]- and [1,11]-bistosyl derivatives of cyclam in a ratio of 8:1. Similarly, the [1,11]-diBoc derivative has been prepared by Lindoy and Dong.[15] for elaboration into dendritic cyclam systems. For our purposes we had the options of trying

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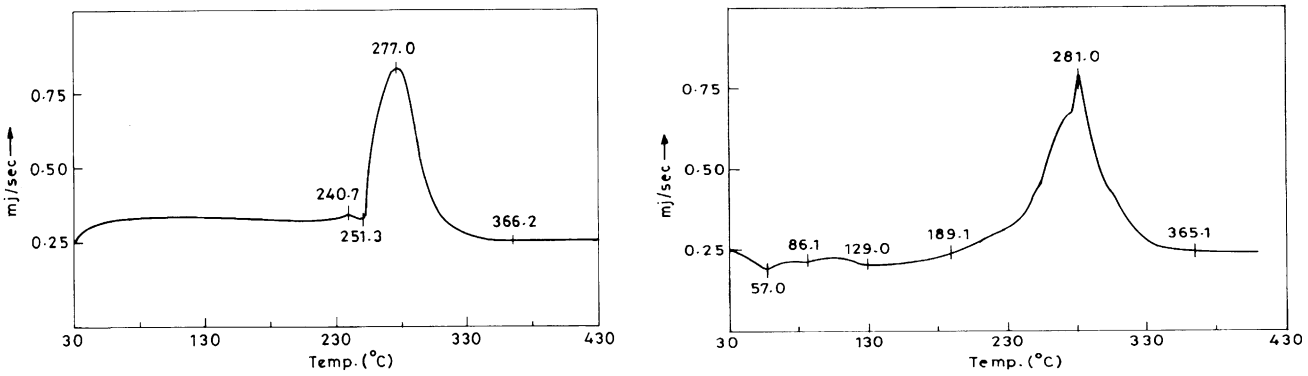
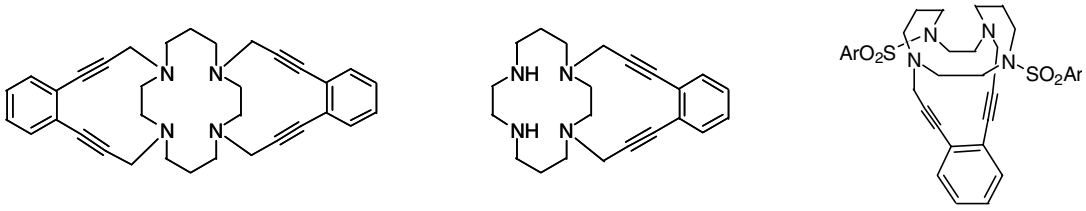


Figure 1. DSC curves for enediyne **2** and its Ni(II)-complex **4**.

to alkylate all four nitrogens of the cyclam with the dibromide **7**[16] or to selectively protect two nitrogens and then alkylate to obtain the monoenediyne derivative. As an initial attempt, an acetonitrile solution of cyclam was treated with 2 equiv of the dibromide **7** at room temperature for 24 h. Although the reaction produced a large number of close running spots as observed by TLC, two of these could be separated by careful column chromatography. The major product was characterized as the bis enediyne **1**, obtained as a brown amorphous powder, while the minor product **2** was the result of incomplete alkylation. The structures of the two products were confirmed by ESI mass spectrometry.

trum of the complex **4** in DMSO-d_6 showed broad signals for the various methylenes; however, there was not much difference in the chemical shift in comparison with the original enediyne **1**, which indicated that the complex could be diamagnetic. The absence of any EPR signal confirmed the diamagnetic nature, which is also consistent with a square planar arrangement. MALDI mass spectral analysis showed a molecular ion peak at m/z 558 (M+Ni) confirming the formation of the complex.

Having successfully synthesized the cyclam-based enediyne **1** and its Ni-complex **4**, we decided to study, (i)



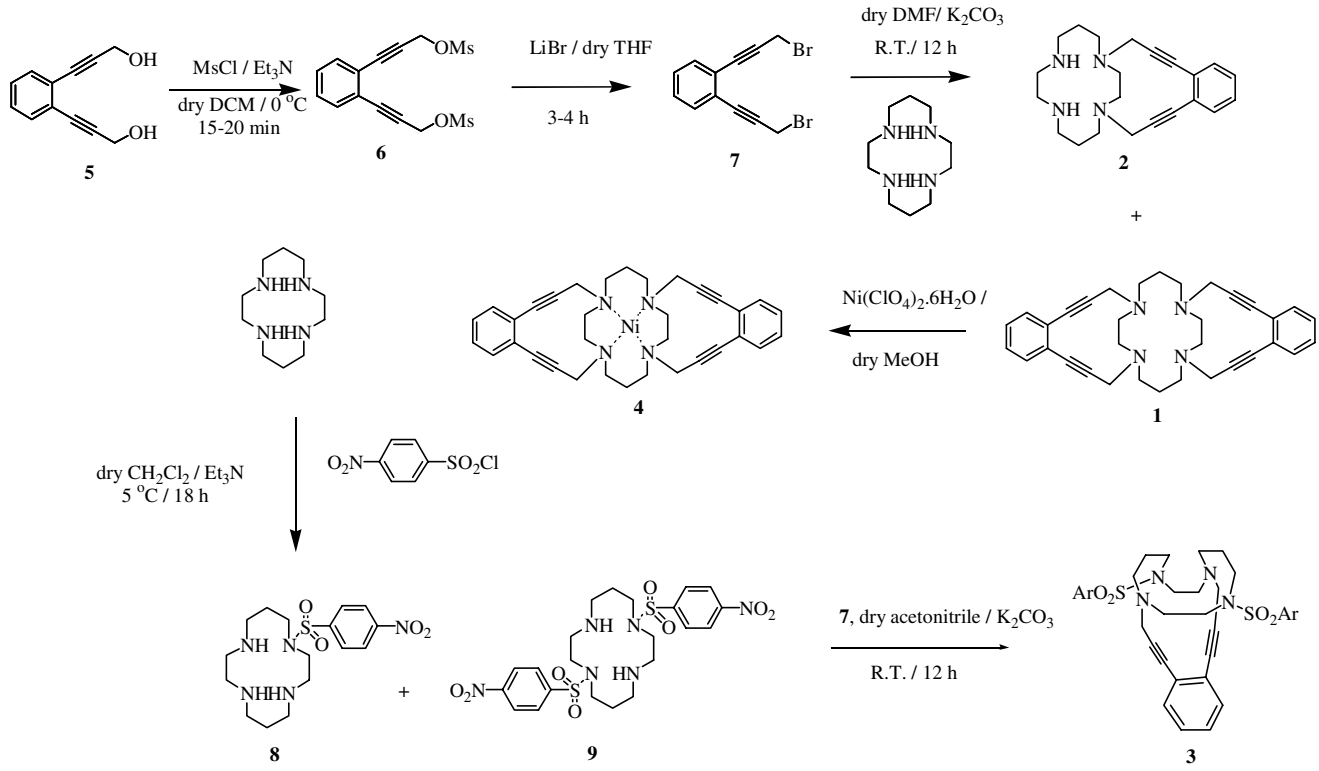
1 **2** **3**

Compound **2** showed a molecular ion peak at m/z 351 while a peak at m/z 501 for compound **1** was in conformity with the proposed structure. The participation of N1 and N11 in alkylation was based on the proton chemical shifts as well as literature precedence.

For the synthesis of the mono-enediyne **3**, bis-4-nitrophenylsulfonyl cyclam **9** was first prepared by treatment of cyclam with 2 equiv of 4-nitrobenzenesulfonyl chloride. The ^{1}H NMR and mass spectrum were fully consistent with the proposed structure of the bis-sulfonamide. Compound **9** was then treated with 1 equiv of the dibromide[7] to provide the cyclam enediyne **3**. Again the structure was confirmed by NMR and mass spectroscopy.

The Ni^{2+} complex of the bis-enediyne **1** was prepared by treatment with a methanolic solution of Ni(II) perchlorate followed by slow evaporation. The ^{1}H NMR spec-

the effect of complexation on the activation barrier to Bergman cyclization (BC), and (ii) the DNA-cleaving ability of the complex **4** under oxidative conditions in view of the similar reactivity of cyclam-metal ion complexes.[17a] A particular point of interest was that, with the incorporation of the enediyne backbone, whether the cyclam complex still retained the cleaving activity.[17b] Regarding the effect on BC, the thermal reactivity of the enediyne **1** and its Ni-complex **4** were studied by differential scanning calorimetry (DSC).[18] The onset temperature for Bergman cyclization (BC) in the neat enediyne was found to be 251 °C, which was significantly lowered upon complexation to Ni(II) for which the onset temperature was observed at 189.1 °C. The thermograms for the parent enediyne **1** and its complex **4** are shown in Figure 1. For clarification of the second point, compound **4** was incubated with supercoiled plasmid DNA pBR322 in the presence of magnesium monoperphthalate (MMPP) as



co-oxidant. Agarose gel electrophoresis revealed the nicking of the ds-DNA by the Ni complex (Lane 1, Fig. 2).[19] A blank experiment was also carried out with the complex in the absence of the co-oxidant for which no cleavage was seen, Lane 2, Figure 2. Thus, the incorporation of the enediyne did not qualitatively perturb the DNA-cleaving ability of the cyclam based complex.

In conclusion, we have, for the first time, synthesized cyclam-based enediynes and showed that complexation to metal ions lowers the onset temperature for BC. We have also demonstrated the DNA-cleaving ability of the Ni-complex under oxidative conditions. Currently, we are investigating the synthesis of similar enediynes with a smaller ring size in order to lower the onset temperature for BC to ambient temperature upon complexation. This will enable us to combine radical mediated DNA-damage by the enediyne and the metal ion mediated oxidative damage of DNA.

Lane 1: DNA in TAE buffer (pH 7.4, 0.4 μm/bp) (7 μl)+complex **4** (0.02 mM, 30 min) in MeOH (5 μl)+MMPP (0.04 mM, 30 min) in MeOH (5 μl)+β-mercaptoethanol (0.12 mM, after 30 min) in MeOH (5 μl) (to terminate the reaction) at 37 °C; lane 2: DNA in TAE buffer (pH 7.4, 0.4 μm/bp) (7 μl)+complex **4** (0.02 mM, 30 min) in MeOH (5 μl) at 37 °C; lane 3: DNA in TAE buffer (pH 7.4, 0.4 μm/bp) (7 μl)+MeOH (10 μl) at 37 °C.

Figure 2. DNA cleavage experiment with the Ni-complex **4**.

Selected spectral data

Cyclam **1**: mp 250–52 °C (dec); δ_H (200 MHz, $CDCl_3$) 7.32 (4H, m, aromatic-*H*), 7.25 (4H, m, aromatic-*H*), 3.56 (8H, s, $4\times CH_2C$), 3.08 (8H, s, NCH_2CH_2N), 2.76 (8H, t, $J = 6.7$ Hz, $NCH_2CH_2CH_2N$), 1.74 (4H, m, $NCH_2CH_2CH_2N$); δ_c (50 MHz, $CDCl_3$) 130.4, 127.8, 126.3, 89.4, 84.6, 52.5, 52.3, 44.5, 24.9; Mass (ES^+): *m/z* 501 (MH^+); HRMS: calcd for $C_{32}H_{36}N_4+H^+$ 501.3021 found 501.2994.

1,14,18,21-Tetraaza-tricyclo[12.10.2.0[5,10]]hexacosa-5(10),6,8-triene-3,11-diyne **2**: viscous brown oil; δ_H (200 MHz, $CDCl_3$) 7.32 (2H, m, aromatic-H), 7.20 (2H, m, aromatic-H), 3.45 (4H, s, $2\times CH_2C$), 3.02 (4H, s, $2\times NCH_2CH_2N$), 2.83 (4H, s, $HNCH_2CH_2NH$), 2.78 (4H, t, $J = 6.2$ Hz, $NHCH_2CH_2CH_2$), 2.65 (4H, t, $J = 6$ Hz, $NCH_2CH_2CH_2$), 1.74 (4H, m, $2\times NCH_2CH_2CH_2$); Mass (ES^+): *m/z* 351.23 (MH^+) HRMS: calcd for $C_{22}H_{30}N_4+H^+$ 351.2551 found 351.2497.

17,23-Bis-(4-nitro-benzenesulfonyl)-1,14,17,23-tetraaza-tricyclo[12.6.6.0[5,10]]hexacosa-5(10),6,8-triene-3,11-diyne **3**: brown powder, mp 260 °C (dec); δ_H (200 MHz, $CDCl_3$) 8.28 (4H, d, $J = 8.6$ Hz, aromatic-*H*), 7.95 (4H, d, $J = 8.6$ Hz, aromatic-*H*), 7.36 (4H, m, aromatic-*H*), 3.8–2.5 (24H, br s, $12\times CH_2$); Mass (ES^+): *m/z* 721 (MH^+), 743 (MNa^+); HRMS: calcd for $C_{34}H_{36}N_6O_8S_2+H^+$ 721.2117 found 721.2205.

1,8-Bis-[4-nitro-benzenesulfonyl]-1, 4, 8,11-tetraazacyclotetradecane **9**: viscous oil; δ_H (200 MHz, DMSO-d_6) 8.43 (4H, d, $J = 7.5$ Hz, aromatic-*H*), 8.11 (4H, d, $J = 7.5$ Hz, aromatic-*H*), 3.27 (4H, br s, NCH_2CH_2NH), 3.16 (4H, br s, $NCH_2CH_2CH_2NH$), 2.96 (4H, br s, NCH_2CH_2NH), 2.87 (4H, br s, $NCH_2CH_2CH_2NH$), 1.90 (4H, br s, $NCH_2CH_2CH_2NH$); δ_c (50 MHz, DMSO-d_6) 150.2, 141.9, 129.3, 124.9, 48.0, 47.2, 46.8, 45.4, 44.7; Mass (ES^+): m/z 571(MH^+).

Ni-complex **4**: brown powder mp 190 °C (dec); δ_H (200 MHz, MeOH-d_4) 7.21 (8H, m, aromatic-*H*), 3.77 (8H, s, NCH_2C), 3.03 (8H, s, $4 \times CH_2$, NCH_2CH_2N), 1.88 (8H, t, $J = 6.7$ Hz, $NCH_2CH_2CH_2N$), 1.24 (4H, m, $NCH_2CH_2CH_2N$); Mass (MALDI) m/z 558 (M+Ni).

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19. The mechanism of DNA cleavage of Ni-cyclam complex **4** has been proposed by Rokita et al.[17a] to involve an Ni(III)-species followed by coordination of the DNA base and subsequent oxidative degradation.