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Acetone promoted 1,4-migration of an alkoxycarbonyl group on a *syn*-1,2-diamine

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ABSTRACT

A 2-protected *cis*-amino mitosene undergoes an irreversible acetone promoted isomerization and converts to the 1-isomer. Kinetic studies and DFT calculations of the reaction are reported. An organocatalytic mechanism is proposed, involving a covalent intermediate formed by reaction of the mitosene and acetone.

Introduction

Mitomycin C (MC)[1] is an antitumor antibiotic used clinically to treat stomach, anal and lung cancers[2] and is the center of numerous research endeavors.[1–12] Its cytotoxicity is believed to be primarily due to DNA interstand crosslinks with a trans stereochemistry (α-ICLs). Decarbamoyl mitomycin C (DMC), a MC analog lacking the carbamate on C10, generates the same α-ICL as MC but also yields a major unique stereoisomeric ICL with a cis stereochemistry (beta isomer, β-ICL, Fig. 1). Both α-and β ICLs are the lesions primarily responsible for the cytotoxicities of MC and DMC.[13] Though both lesions share similar features, DMC is more toxic to human cancer cells than MC and induces apoptosis efficiently in a p53 independent manner.[14]

Access to mitosene-alpha and mitosene-beta DNA-adducts is essential to elucidate if and how the local DNA structure of these adducts is responsible for the different biochemical responses displayed by the two drugs. Such substrates have been previously used to investigate the mechanisms involved in the repair of mitomycin C mono- and interstrand cross-linked DNA adducts[6] and to determine how MC and DMC induce p53-independent $p21^{WAF1/Clp1}$ activation in p53 proficient and p53 deficient cancer cells.[15]

MC-DNA adducts (α-ICLs) are easily obtained *via* a biomimetic route, contrary to DMC-DNA adducts (β-ICLs). We have recently developed a route to an amino-mitosene with *cis*-stereochemistry which can be used to generate a cis MC-DNA monoadduct *via* post-oligomerization synthesis (Scheme 1).[16] This chemistry paves the way to the synthesis of β-ICLs.

Synthesis of the *cis*-amino mitosene precursor **1** led to an unforeseen discovery: during the reduction of the azide precursor *via* a Staudinger reaction, the desired *cis*-triamino mitosene **1** was often accompanied by a novel mitosene **2** with similar mass and spectroscopic characteristics as **1**.

Unexpected reactions and rearrangements from *cis*-amino mitosenes have been previously described. Relevant to the findings presented here is the *O* to *N* migration of the acetyl group from the *cis*-acetoxyaminomitosene to the *cis*-acetylamino-hydroxymitosene during the solvolysis of MC with glacial acetic acid[17] and the *O* to *N* migration of an acyl group in the reaction of MC with trifluoroacetic acid (Scheme 2).[18]

Additionally, an oxazolidinone derivative of *cis*-1-hydroxy-2,7-diaminomitosene resulting from an intramolecular reaction

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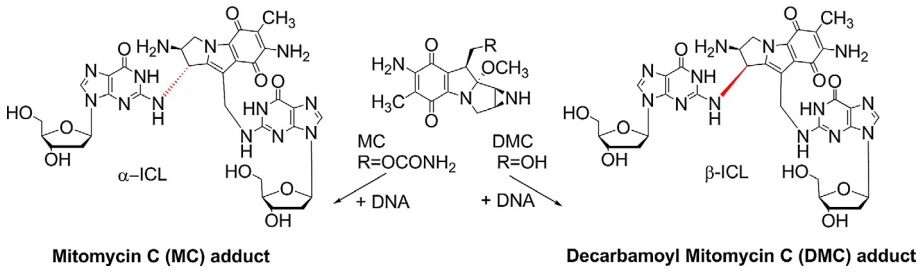
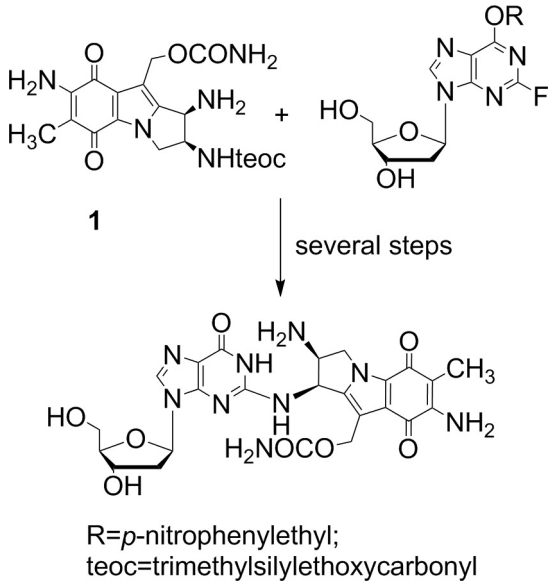
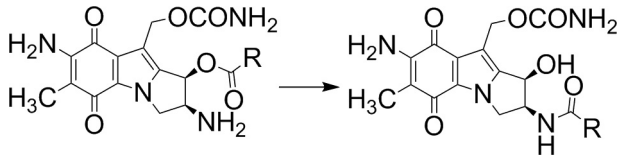


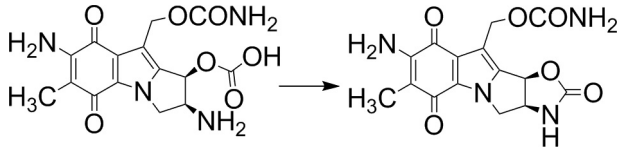
Fig. 1. Mitomycin C (MC) and Decarbamoyl Mitomycin C (DMC) interstrand cross links.



Scheme 1. Synthesis of a beta MC-DNA monoadduct *via* a *cis*-triaminomitosene.



Scheme 2. Acyl migration on *cis*-acyloxymitosenes to form N-acylmitosenes (R = CH_3, CF_3).



Scheme 3. Formation of an oxazolidinone derivative of *cis*-1-hydroxy-2,7-diaminomitosene.

between the adjacent 1,2 cis carbonate and amino groups was recently characterized (Scheme 3).[19]

Results and discussion

In line with these previous findings, we report here the acetone promoted migration of a 2-trimethylsilylethoxycarbonyl (teoc)-group on the *cis*-triaminomitosene **1**, yielding the novel mitosene **2** (Scheme 4).

Compound **2** was first detected during the isolation of **1** by chromatography. HRMS analysis revealed a molecular formula and molecular weight identical to that of the desired *cis*-triamino mitosene strongly suggesting that compound **2** was an isomer of **1**. Due to the limited availability of MC we devoted some time to maximize the yield of the novel adduct for NMR characterization. The formation of **2** was observed only when acetone was used for the isolation of **1**. This prompted us to investigate if acetone itself was involved in the formation of **2**. A solution of **1** in methanol and DMSO was prepared without using acetone and was monitored by NMR. Compound **1** was stable and no trace of **2** was observed. Upon addition of acetone, the disappearance of **1** and formation of **2** were observed. This proved that acetone was involved in the conversion of **1** to **2** and allowed us to synthesize enough **2** for characterization. The UV spectrum of the novel compound showed the maximum absorbance at 252 and 310 nm characteristics of the mitosene chromophore (supplementary information, Fig. S10). The relative stereochemistry of many 1-substituted 2-aminomitosenes has also been assigned using circular dichroism, using the sign of the Cotton effect at 520–550 nm as diagnosis.[20] The CD spectrum of **2** followed this general rule as **2** exhibited a weak positive cotton effect around 550 nm as expected for a cis configuration (supplementary information, Fig. S11).

The ^1H and ^{13}C NMR in DMSO-d_6 of the new mitosene showed the expected peaks for all hydrogens and carbons. NOESY, HSQC, COSY and DEPT experiments allowed the correct assignment of all carbons and protons (supplementary information; Figs. S5–S8). Noteworthy is the dramatic upfield shift (3.25 ppm) of the signal for the amide proton in the ^1H NMR spectrum upon migration of the teoc group from N_2 to N_1 along with the downfield shift of H_1 and H_2 signals (Fig. 2). In addition, splitting of the amide signal at a 2:1 ratio indicates that **2** exist as rotamers in solution, this latter phenomenon likely due to the newly hindered free rotation around the NH-C(O) bond (Fig. 2). Variable temperature NMR experiments show a coalescence of the 2 signals at T = 60 °C (Fig. S12). NOE and COSY experiments showed both direct and through-space correlations between the amide proton and H_1, confirming the position of the teoc group on N_1.

We then investigated the kinetics of formation of **2** both in pure acetone-d_6 and in DMSO-d_6: acetone-d_6 (1:10) by NMR spectroscopy. The formation of **2** was not a direct mechanism as expected. Instead a third compound, compound **X**, was transiently observed but could not be isolated (Scheme 4). The concentrations of the 3 species in solution (**1**, **2** and **X**) were calculated over time using qNMR (Mnova software; Mestrelab) in both solvents (pure acetone-d_6 and DMSO-d_6: acetone-d_6) (Fig. 3). The formation of **2** in pure acetone-d_6 consists of two consecutive steps (with k_{1obsA} and k_{2obsA} being the associated rate constants). The first step is extremely fast, (*i.e.* all of the **1** initially present is rapidly converted into **X**) and appears to follow a first order rate with $k_{1obsA} = 0.145\ min^{-1}$ (supplementary material, kinetic-calculations). Compound **X** is