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THERMAL ATROPISOMERISM OF FULLY FUNCTIONALIZED VANCOMYCIN CD, DE, AND CDE RING SYSTEMS

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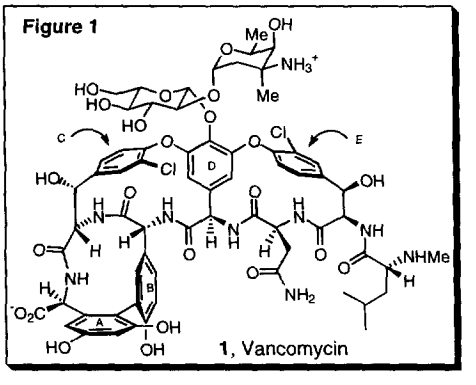
Abstract. A study of the thermal atropisomerism of fully functionalized vancomycin CD, DE and CDE ring systems is detailed. The studies suggested and resulted in the realization of a selective DE ring system atropisomerism of a fully functionalized vancomycin CDE ring system, offering a unique solution to the control of natural product atropisomer stereochemistry. © 1997 Elsevier Science Ltd.

Vancomycin (**1**, Fig. 1) is the prototypical member of a class of clinically important glycopeptide antibiotics.[1-3] Currently, vancomycin is the therapeutic agent of choice for the treatment of methicillin-resistant *Staphylococcus aureus* and is routinely used against enterococci and bacterial infections in patients allergic to β-lactam antibiotics.[4] The structural complexity of vancomycin, the interest in defining the structural features responsible for inhibition of cell wall biosynthesis in sensitive bacteria,[5] and the emergence of clinical resistance[6] have provided renewed interest in the total synthesis of **1** and related agents.[7-11]

Figure 1

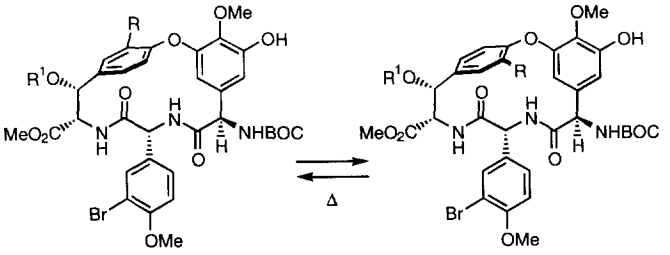


1, Vancomycin

In recent efforts, we described the synthesis of the fully functionalized vancomycin CD and DE ring systems and detailed the first disclosure of their thermal atropisomerism.[9,10] In contrast to past studies conducted at lower temperatures, the thermal interconversion of the CD and DE ring system atropisomers was found to proceed rapidly at temperatures of ≥155 °C and more slowly at 140 °C. This allowed the undesired atropisomers to be thermally equilibrated, chromatographically reisolated, and recycled to provide the desired atropisomers. The precursor CD and DE nitro derivatives were found to be equilibrated more rapidly than the corresponding chloro atropisomers and the rate of isomerization could be controlled not only by the choice of temperature but also by the choice of solvent. Significantly, the DE atropisomer equilibration occurred much more rapidly than that of the CD ring system. This suggested that it may be possible to preferentially equilibrate the vancomycin DE versus CD atropisomers within an intact CDE ring system and that this may be best conducted with a DE aryl nitro intermediate containing the installed CD aryl chloride. This further suggested a preferred order to the synthetic introduction of the CD and DE

ring systems in which the CD ring system is assembled first and the atropisomer stereochemistry set with equilibration of its aryl nitro derivative. Following conversion to the CD aryl chloride, introduction of the DE ring system and subsequent selective DE atropisomer equilibration would allow a unique solution to the control of vancomycin CDE atropisomer stereochemistry. Herein, we detail further studies on the thermal atropisomerism of alternatively substituted but fully functionalized vancomycin CD and DE ring systems that further define its scope and the realization of a selective DE atropisomerism of a fully functionalized CDE ring system.

CD Ring System. The thermal atropisomer equilibrations of **2**, **3**, and **4** were examined and constitute fully functionalized derivatives of the vancomycin CD ring system.[9] The protected alcohols **2** and **3** incorporating an aryl nitro or chloro substituent were found to most rapidly equilibrate in DMSO and DMF and to do so much more slowly in *o*-$Cl_2C_6H_4$, Table 1. Even in DMSO, little or no equilibration was observed at 120 °C, slow equilibration



2a, R = NO_2 R^1 = TBDMS 1.1 : 1 **2b**, R = NO_2 R^1 = TBDMS
3a, R = Cl R^1 = TBDMS 1.2 : 1 **3b**, R = Cl R^1 = TBDMS
4a, R = NO_2 R^1 = H **4b**, R = NO_2 R^1 = H

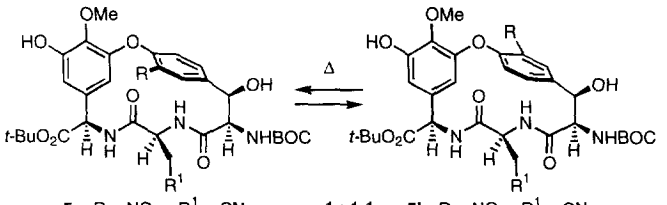
Table 1.

Compd	Conditions	k (h^{-1})	$t_{1/2}$ (h)
2	155 °C, DMSO	0.27	1.06
2	140 °C, DMSO	0.082	3.52
2	140 °C, *o*-$Cl_2C_6H_4$	0.029	9.77
3	140 °C, DMSO	0.071	4.03
3	140 °C, *o*-$Cl_2C_6H_4$	0.0054	53.0

for **2** (DMSO): E_a = 26.6 kcal/mol, $\Delta H^{\ddagger}$ = 27.0 kcal/mol, $\Delta S^{\ddagger}$ = -1.7 eu, $\Delta G^{\ddagger}$(130 °C) = 27.7 kcal/mol

was observed at 140 °C, and rapid equilibration was observed at 155 °C. The nitro derivative **2** equilibrated more rapidly than the corresponding chloro derivative **3**. In contrast, the free alcohol **4** failed to undergo clean atropisomerism in either DMSO or *o*-$Cl_2C_6H_4$ (140 °C). Although this was not investigated in detail, retro Aldol ring cleavage was contributing in part to this inability to cleanly thermally equilibrate the CD ring system.[12] This led to adoption of a synthetic approach to the CD[9,10] and CDE[13] ring systems that incorporates and preserves protection of the alcohol despite potential challenges this introduces for macrocyclization via biaryl ether formation.[9,13]

DE Ring System. The thermal atropisomer equilibrations of a series of derivatives of the fully functionalized vancomycin DE ring system **5–8** were examined, Table 2. This includes the initial nitro and chloro derivatives **5** and **6** we have described[9] incorporating the asparagine (Asn) residue carboxamide protected as a nitrile as well as more recent derivatives[13] incorporating the free and (4,4′-dimethoxydiphenyl)methyl (Ddm) protected carboxamide. All the derivatives contain the free alcohol of the corner β-hydroxyphenylalanine subunit and, unlike the CD ring system, were found to withstand thermal atropisomerism conditions without evidence of competitive or problematic retro Aldol ring cleavage. Analogous to observations made with the CD ring system, the nitro derivative **5** equilibrated more readily than the corresponding chloro derivative **6**. Unlike the CD ring system, the equilibration was remarkably rapid and proceeded readily even at 120–130 °C. As such, the choice of solvent had



5a, R = NO_2 R^1 = CN 1 : 1.1 **5b**, R = NO_2 R^1 = CN
6a, R = Cl R^1 = CN 1 : 1 **6b**, R = Cl R^1 = CN
7a, R = NO_2 R^1 = CONHDdm 1.3 : 1 **7b**, R = NO_2 R^1 = CONHDdm
8a, R = NO_2 R^1 = $CONH_2$ 1.3 : 1 **8b**, R = NO_2 R^1 = $CONH_2$

for **5** (DMSO): E_a = 15.3 kcal/mol
$\Delta H^{\ddagger}$ = 14.5 kcal/mol, $\Delta S^{\ddagger}$ = -24.0 eu, $\Delta G^{\ddagger}$(130 °C) = 24.2 kcal/mol
for **5** (*o*-$Cl_2C_6H_4$): E_a = 16.4 kcal/mol
$\Delta H^{\ddagger}$ = 15.2 kcal/mol, $\Delta S^{\ddagger}$ = -22.0 eu, $\Delta G^{\ddagger}$(130 °C) = 24.1 kcal/mol
for **7** (DMSO): E_a = 17.1 kcal/mol
$\Delta H^{\ddagger}$ = 16.8 kcal/mol, $\Delta S^{\ddagger}$ = -17.3 eu, $\Delta G^{\ddagger}$(130 °C) = 23.8 kcal/mol

Table 2.

Compd	Conditions	k (h^{-1})	$t_{1/2}$ (h)
5	130 °C, DMSO	0.66	0.23
5	140 °C, DMSO	1.05	0.17
5	130 °C, *o*-$Cl_2C_6H_4$	0.70	0.29
5	140 °C, *o*-$Cl_2C_6H_4$	1.15	0.15
6	140 °C, DMSO	0.52	0.39
7	120 °C, DMSO	0.58	0.43
7	130 °C, DMSO	1.5	0.17
7	140 °C, DMSO	1.7	0.15
8	125 °C, DMSO	0.88	0.28
8	140 °C, DMSO	2.06	0.092

for **8** (DMSO): E_a = 18.5 kcal/mol, $\Delta H^{\ddagger}$ = 17.9 kcal/mol
$\Delta S^{\ddagger}$ = -14.3 eu, $\Delta G^{\ddagger}$(130 °C) = 23.7 kcal/mol

a less pronounced effect on the apparent ease of atropisomerism. The nature of the Asn residue substituent had little impact on this rapid rate of atropisomerism, and the Ddm protected carboxamide **7** as well as the free carboxamide **8** isomerized at rates comparable with **5**. Interestingly, the thermal atropisomerism of the free carboxamide **8** was observed without competitive Asn–isoaspartate rearrangement analogous to that observed in the acidic, thermal degradation (pH 4.2, 70–80 °C, 40 h) studies of vancomycin leading to CDP-1.[14]

CDE Ring System. Consistent with projections, the thermal atropisomerism of a fully functionalized vancomycin CDE ring system[13] bearing a CD chloro substituent and a DE nitro substituent with a protected alcohol in the CD ring system was examined and found to proceed with clean DE versus CD atropisomer isomerization, Table 3. Although considerably slower than the DE ring systems **5–8** themselves, no competitive retro Aldol ring opening was detected and exclusive isomerization of only the DE atropisomers and not the CD atropisomers was observed to provide a 1:1 mixture of **9a**:**9b** in DMSO (140 °C, $t_{½}$ = 3.1 h) or in *o*-$Cl_2C_6H_4$ at 130 or 140 °C ($t_{½}$ =

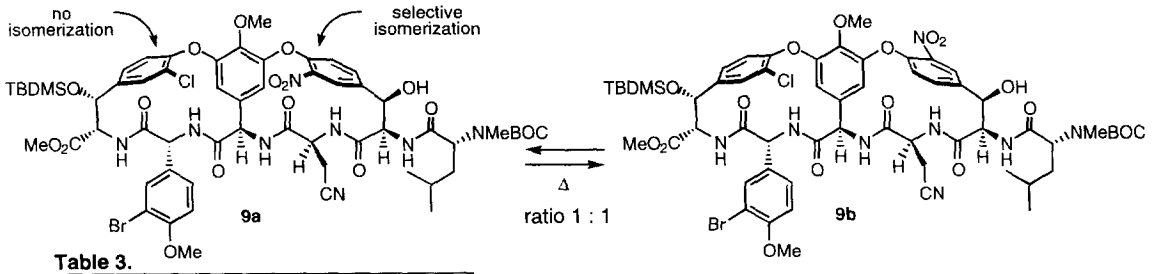


Table 3.

Compd	Conditions	k (h^{-1})	$t_{1/2}$ (h)
9	130 °C, *o*-$Cl_2C_6H_4$	0.013	20.4
9	140 °C, *o*-$Cl_2C_6H_4$	0.029	9.3
9	140 °C, DMSO	0.093	3.1

for **9** (*o*-$Cl_2C_6H_4$): E_a = 25.0 kcal/mol
$\Delta H^{\ddagger}$ = 24.2 kcal/mol, $\Delta S^{\ddagger}$ = -7.8 eu, $\Delta G^{\ddagger}$(140 °C) = 27.4 kcal/mol

20.4 and 9.3 h, respectively). This permitted the sequential synthesis of the CD ring system with thermal equilibration and control of its atropisomer stereochemistry followed by DE ring closure to provide the fully functionalized CDE ring system. Selective thermal equilibration of the undesired atropisomer **9a** that was most cleanly effected in *o*-$Cl_2C_6H_4$ (140 °C), reseparation, and recycling permits the requisite control of the CDE atropisomer stereochemistry.[15]

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12. The retro Aldol product (>10%) and five additional minor products appear early in the course of the thermal isomerization. Comparable side reactions are not observed with **2** and **3**. For **4** (DMSO, 140 °C), approximate $k = 0.086\ h^{-1}$, $t_{1/2} = 2.52$ h, **4a**:**4b** = 1.6:1.
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15. The atropisomerism was followed by ^1H NMR in deuterated solvents, see ref 9.

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