bilization. The density of vibrational states of the deuterated complex will be larger, while the Ni–C_3H_6 and Ni–C_3D_6 bond energies will be very similar, so we would expect longer lifetimes (and greater stabilization efficiency) for the Ni + C_3D_6 reaction in a termolecular mechanism.

In an attempt to clarify the nature of the Ni + alkene products, we gently focused excimer laser pulses at 308 and 248 nm (two-photon energy of 8.1 and 10.0 eV) downstream in the flow tube and analyzed the resulting cations in a quadrupole mass spectrometer. The only photoion observed is Ni$^+$. It is plausible that collisionally stabilized, π-bonded Ni–alkene complexes photodissociate to Ni + alkene and that subsequent two-photon ionization of Ni produces the observed Ni$^+$.

The ground-state configurations[12] of Fe, Co, and Ni are $3d^{n-2}4s^2$. The $4s^2$ occupancy and the large spatial extent of 4s relative to 3d give these atoms closed-shell character at long range. Accordingly, ab initio calculations[10,11] find that M($d^{n-2}s^2$) + C_2H_4 asymptotes produce only repulsive potentials. Substantial M–C_2H_4 binding arises only from excited-state $d^{n-1}s$ asymptotes. In Fe, Co, and Ni, the lowest energy high-spin $d^{n-1}s$ levels lie at excitation energies of 20, 10, and 0.6 kcal/mol, respectively. The lowest energy low-spin $d^{n-1}s$ levels lie at 34, 21, and 10 kcal/mol.[12]

The challenge for $d^{n-2}s^2$ reactants is to reach sufficiently short M–alkene approach distances to access attractive $d^{n-1}s$ potential surfaces before deflecting off the repulsive wall of the $d^{n-2}s^2$ surface. The attractive surfaces will often have different spin multiplicity from the reactants.[10,15] The avoided intersection between the repulsive $d^{n-2}s^2$ surface and the attractive $d^{n-1}s$ surface can produce a barrier on the lowest energy adiabatic surface whose height should be roughly proportional to the atomic excitation energy from $d^{n-2}s^2$ to $d^{n-1}s$. Thus the strength of M–alkene binding and the energy of the surface intersections combine to determine the gas-phase reactivity.

Measurement of gas-phase rate constants at 300 K with well-defined initial metal atom states can provide quantitative experimental insights into gas-phase M–alkene interactions. Assuming Arrhenius behavior $k(T) = k_{hs} \exp(-E/k_BT)$ with preexponential factor equal to the hard-spheres collision rate k_{hs} (the largest plausible value),[13] we can convert the measured reaction probabilities $P = k(300\ \mathrm{K})/k_{hs}$ to *upper bounds* E_{max} on the activation energy E using the equation $E_{max} = -k_BT \ln P$.[5b] In addition, those reactions that occur at measurable rate exhibit exponential decay of the M reactant over at least one decade. In the termolecular stabilization mechanism, this implies at least 10–15 kcal/mol of M–alkene binding energy relative to ground-state reactants, depending on the entropy change at 300 K and on the alkene number density required to effect the 10-fold decay of M atom density.[3] No reaction ($k < 10^{-14}$ cm^3·s^{-1}) implies either an activation energy in excess of 6 kcal/mol or a M–alkene binding energy less than 10–15 kcal/mol relative to ground-state reactants, or both.

Since Fe and Co ground states are unreactive, we conclude that they never reach the potential wells arising from $d^{n-1}s$ asymptotes or that the wells are not sufficiently deep. This is consistent with the minor shifts between vibrational frequencies of C_2H_4 and FeC_2H_4 in matrix IR spectra[6b] and with ab initio calculations[10a] that find a bound Fe–C_2H_4 complex lying 6 kcal/mol *above* Fe(d^6s^2,^{5}D) + C_2H_4. Since the Cu($d^{10}s$,^{2}S) ground state is well isolated from excited states, we expect no surface intersections (no potential barrier) for Cu + alkene. The absence of measurable Cu + alkene reaction implies binding energies less than 10–15 kcal/mol, consistent with a recent calculated Cu–C_2H_4 binding energy of 8 kcal/mol obtained with core pseudopotentials.[11]

NiC_2H_4 is observed in cryogenic matrices;[7] the C_2H_4 vibrational frequencies are more strongly perturbed in NiC_2H_4 than in FeC_2H_4. Only the repulsive Ni–C_2H_4 surfaces arise from the Ni(d^8s^2,^{3}F) ground state. Early ab initio work[9] found a triplet NiC_2H_4 ground state ($^3A_1$) from Ni(d^9s,^{3}D). Recent calculations[10b] with more extensive basis sets find the same triplet surface to be repulsive. Ni(d^9s,^{1}D) + C_2H_4 gives an attractive *singlet* surface ($^1A_1$) bound by 10 kcal/mol relative to ground-state Ni + C_2H_4.[12]

The observed extent of the Ni(d^9s,^{3}D) + alkene reactions indicates Ni–alkene binding energies in excess of 10–15 kcal/mol, consistent with the recent Ni–C_2H_4 calculations.[10b] Apparently Ni(d^9s,^{3}D) + C_2H_4 collisions at 300 K readily access the $^1A_1$ potential well. The reaction efficiencies indicate very small barriers on the *adiabatic* surface which has $^3A_1$ character at long range and $^1A_1$ character at short range. Reaction probabilities of $^1/_{500}$ for Ni + ethene, $^1/_{25}$ for Ni + propene, and $^1/_2$ for Ni + 1-butene imply activation energies *not larger than* 3.5, 1.9, and 0.4 kcal/mol, respectively. For Ni + C_2H_4, the calculations[10b] find the crossing point between the $^3A_1$ surface and the $^1A_1$ surface to lie ~8 kcal/mol above Ni(d^9s,^{3}D) + C_2H_4, which is probably an overestimate.

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Room Temperature Generation of Reactive Intermediates $Cp^*_2Zr{=}O$ and $Cp^*_2Zr{=}S$: Trapping Reactions with Unsaturated Organic Molecules and Dative Ligands

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We provided evidence recently that the reactive intermediate [$Cp^*_2Zr{=}O$] is generated at 160 °C by α-elimination of benzene from $Cp^*_2Zr(Ph)(OH)$.[1,2] The oxo intermediate reacts with selected alkynes, but at this elevated temperature the materials isolated presumably result from rearrangement of the initially formed alkyne addition products. We now report a novel room-temperature route to [$Cp^*_2Zr{=}O$].[3] This reaction allows isolation of oxametallacycles that result from initial reaction of the oxo complex with alkynes and provides a means of utilizing alkyl- as well as aryl-substituted acetylenes in the reaction. In addition, we have found a mild route to the analogous sulfido complex [$Cp^*_2Zr{=}S$]. Like its oxo analogue, this material undergoes cycloaddition reactions with alkynes and nitriles; in this case, we have also been able to trap the reactive species with dative ligands.

Treatment of $Cp^*_2Zr(OH)(Cl)$ (**1**)[4] with 1 equiv of $AgOSO_2CF_3$ produces $Cp^*_2Zr(OH)(OSO_2CF_3)$ (**2**) in nearly quantitative yield by ^{1}H NMR (Scheme I).[5] Deprotonation of **2** with the hindered base $KN(Si(CH_3)_3)_2$ leads to the successful generation of [$Cp^*_2Zr{=}O$] as judged by its subsequent trapping with various alkynes and nitriles. A critical example involves diphenylacetylene. The metallacycle complex **3a** was prepared recently by Hillhouse upon treatment of the zirconocene diphenylacetylene complex $Cp^*_2Zr(PhCCPh)$ with N_2O.[6] We were

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(1) Carney, M. J.; Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 8751.

(2) For studies on the chemistry of related reactive complexes with metal–X multiple bonds, see: (a) Klein, D. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 3079. (b) Glueck, D. S.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 2719. (c) Walsh, P. J.; Hollander, F. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 8729. (d) Cummins, C. C.; Baxter, S. M.; Wolczanski, P. T. *J. Am. Chem. Soc.* **1988**, *110*, 8731.

(3) For excellent reviews on the synthesis and chemistry of oxo complexes, see: (a) Nugent, W. A.; Mayer, J. A. *Metal–Ligand Multiple Bonds*; Wiley-Interscience: New York, 1988. (b) Holm, R. H. *Chem. Rev.* **1987**, *87*, 1401 and references therein.

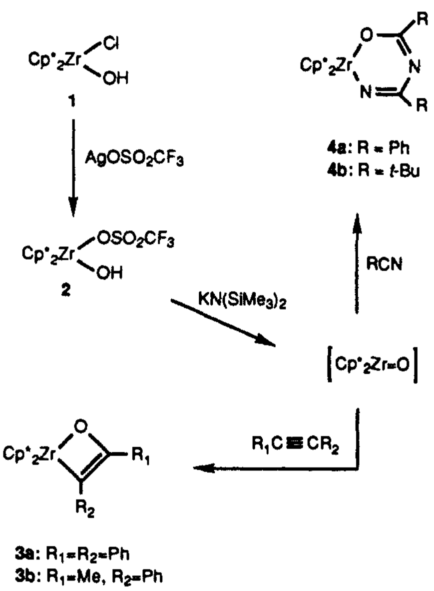
(4) (a) Hillhouse, G. L.; Bercaw, J. E. *J. Am. Chem. Soc.* **1984**, *106*, 5472. (b) Bortolin, R.; Patel, V.; Munday, I.; Taylor, N. J.; Carty, A. J. *J. Chem. Soc., Chem. Commun.* **1985**, 456.

(5) Spectroscopic and analytical data on the new compounds described here are provided as supplementary information.

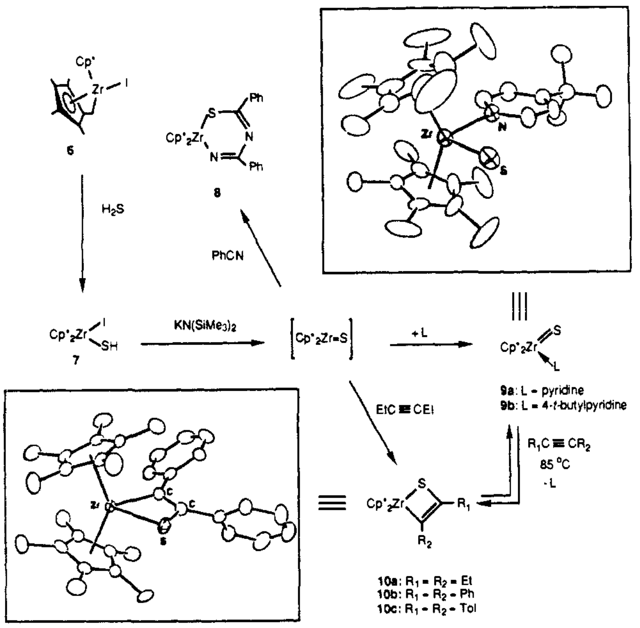
(6) Vaughan, G. A.; Sofield, C. D.; Hillhouse, G. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1989**, *111*, 5491.

0002-7863/90/1512-6426$02.50/0

Scheme I



Scheme II



not able to detect this expected trapping product on thermal decomposition of $Cp^*_2Zr(Ph)(OH)$ at 160 °C in the presence of diphenylacetylene, presumably due to the rearrangement of **3a** at this temperature.[1] In contrast, deprotonation of **2** in the presence of excess diphenylacetylene cleanly affords **3a**. Also, deprotonation of **2** in the presence of the unsymmetrical alkyne 1-phenyl-1-propyne (a reaction that led only to decomposition products upon thermolyzing $Cp^*_2Zr(Ph)(OH)$) also occurs cleanly and yields only one isomer of **3b** (by ^1H NMR). The regiochemistry was confirmed by treatment of **3b** with 2 equiv of H_2O, yielding phenylacetone[7] uncontaminated by $PhCOCH_2CH_3$.[8] Further, deprotonation of **2** in the presence of benzonitrile or trimethylacetonitrile gives the six-membered metallacycles **4a** and **4b**, respectively, in good yield. Complex **4a** is identical with that produced by the thermolysis of $Cp^*_2Zr(Ph)(OH)$ at 160 °C in the presence of excess benzonitrile;[1] the alkyl-substituted metallacycle **4b** apparently does not survive the high-temperature generation procedure.

Encouraged by these results, we attempted to isolate a stable $Cp^*_2(L)Zr{=}O$ species by carrying out the low-temperature generation of $Cp^*_2Zr{=}O$ in the presence of dative ligands to produce compounds analogous to $Cp_2(L)Zr{=}N(t\text{-}Bu)$.[2c] Thus far, these attempts have not been successful. However, we have been able to generate and trap $Cp^*_2Zr{=}S$, an isoelectronic analogue of $Cp^*_2Zr{=}O$. This was accomplished via the route shown in Scheme II, involving room-temperature dehydrohalogenation of $Cp^*_2Zr(SH)(I)$ (**7**).

The high-yield synthesis of cyclometalated iodide **6** (Scheme II) is analogous to that used by Bercaw et al. in the preparation of $(\eta^2\text{-}C_5Me_5)(\eta^5,\eta^1\text{-}C_5Me_4CH_2)HfI$.[9] Complex **7** is most easily generated by treatment of **6** with 1 equiv of H_2S. Dehydrohalogenation of **7** with $K(N(SiMe_3)_2)$ in the presence of benzonitrile affords metallacycle **8** in 79% yield, strongly suggesting that $[Cp^*_2Zr{=}S]$ is generated in this reaction. This conclusion is confirmed by dehydrohalogenation of **7** in the presence of pyridines, from which monomeric terminal sulfido complexes **9a** and **9b** are isolated in 70–80% yield. An X-ray crystal structure determination[10] of **9b** confirmed this Zr=S bonding mode and is shown in Scheme II. The Zr–S distance of 2.316 (1) Å is shorter than known Zr–S single bonds, which typically range from 2.42 to 2.50 Å.[11]

Deprotonation of **7** in the presence of excess 3-hexyne yields metallacyclobutene **10a**. Interestingly, dehydrohalogenation of **7** in the presence of excess diarylacetylenes does not produce the corresponding metallacyclobutenes **10b** and **10c**, but instead yields complex mixtures of products (^1H NMR). However, heating terminal sulfido complex **9a** at 85 °C with 3–4 equiv of diphenyl- or di-*p*-tolylacetylene affords metallacycles **10b** and **10c** in good yield. Most surprisingly, heating **9a** in the presence of excess 3-hexyne yields an equilibrium mixture of **10a** and **9a**; this apparent reversibility was confirmed by warming (45 °C for 2 h) pure metallacycle **10a** with 3 equiv of pyridine, resulting in the clean and nearly complete conversion of **10a** to terminal sulfide **9a** (>95% by ^1H NMR), with concomitant liberation of 3-hexyne. Because of this facile reversibility, we felt it was necessary to confirm the metallacycle structure of **10**, and this was accomplished by an X-ray diffraction study on complex **10b**.[10] An ORTEP diagram of **10b**, shown in Scheme II, clearly demonstrates the presence of a carbon–sulfur bond (C–S = 1.829 (5) Å), while the observed Zr–S distance of 2.505 (1) Å is now more typical of a Zr–S single bond. This structure determination confirmed the proposed formulation of compounds **10a–c** as metallacyclobutenes rather than sulfido–alkyne adducts.[12]

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[7] This assignment was made by comparison of the ^1H NMR spectrum with that of an authentic sample of phenylacetone.

[8] This anti-Markovnikov regiochemistry is analogous to that observed for the cycloaddition of 1-phenyl-1-propyne to the Zr=N bond of $Cp_2Zr{=}N(t\text{-}Bu)$ (ref 2c).

[9] Bulls, A. R.; Schaefer, W. P.; Serfas, M.; Bercaw, J. E. *Organometallics* **1987**, *6*, 1219. The synthesis of **6** begins by treatment of $Cp^*_2ZrI_2$ with 1.0 equiv of neopentyllithium, giving $Cp^*_2Zr(CH_2CMe_3)(I)$ (**5**) in 90% yield. Heating this iodide at 140 °C for 3 h results in elimination of neopentane followed by cyclometalation to give **6** (81% yield).

[10] The X-ray diffraction studies were carried out at the University of California Berkeley College of Chemistry X-ray diffraction facility (CHEXRAY) with Mo Kα (λ = 0.71073 Å) radiation at −82 °C. Crystal data for **9a**: $P2_1/c$, $V = 2811$ (2) Å^3, $\mu = 4.7$ cm^{-1}, $d_{calcd} = 1.25$ g cm^{-3}, $a = 9.753$ (3) Å, $b = 14.829$ (2) Å, $c = 19.438$ (4) Å, $\beta = 90.92$ (3)°, $Z = 4$; the final residuals for 289 variables refined against the 2572 data for which $F^2 > 3.5\sigma(F^2)$ were $R = 0.0658$, $R_w = 0.0845$, and GOF = 3.33. The R value for all 3669 data was 6.58%. Crystal data for **10b**: $Pna2_1$, $V = 2891.2$ (21) Å^3, $\mu = 4.62$ cm^{-1}, $d_{calcd} = 1.31$ g cm^{-3}, $a = 17.143$ (4) Å, $b = 12.566$ (2) Å, $c = 13.421$ (3) Å, $Z = 4$; the final residuals for 324 variables refined against the 1773 data for which $F^2 > 3.0\sigma(F^2)$ were $R = 0.0226$, $R_w = 0.0289$, and GOF = 1.30. The R value for all 1983 data was 2.77%. Details of the structure determinations are provided as supplementary information.

[11] For representative Zr–S distances, see: (a) Kovacs, J. A.; Bergman, R. G. *J. Am. Chem. Soc.* **1989**, *111*, 1131. (b) Hey, E.; Lappert, M. F.; Atwood, J. L.; Bott, S. G. *J. Chem. Soc., Chem. Commun.* **1987**, 421. (c) Bottomley, F.; Drummond, D. F.; Egharevba, G. O.; White, P. S. *Organometallics* **1986**, *5*, 1620. (d) Coucouvanis, D.; Lester, R. K.; Kanatzidis, M. G.; Kessissoglou, D. P. *J. Am. Chem. Soc.* **1985**, *107*, 8279. (e) Coucouvanis, D.; Hadjikyriacou, A.; Kanatzidis, M. G. *J. Chem. Soc., Chem. Commun.* **1985**, 1224.

[12] Several rhenium–oxo–alkyne complexes are known; see, for example: (a) Brower, D. C.; Tonker, T. L.; Morrow, J. R.; Rivers, D. S.; Templeton, J. L. *Organometallics* **1986**, *5*, 1093 (we are grateful to a referee for calling our attention to this paper). (b) Mayer, J. M.; Thorn, D. L.; Tulip, T. H. *J. Am. Chem. Soc.* **1985**, *107*, 7454.

The ready reversibility of the sulfametallacycle (**10a**)-terminal sulfide (**9a**) transformation suggests that $\mathrm{Cp_2^*Zr{=}S}$ is more stable than $\mathrm{Cp_2^*Zr{=}O}$ with respect to cycloaddition with alkynes. We are presently exploring the reactivity of these terminal oxo and sulfido complexes with other unsaturated organic fragments such as olefins, aldehydes, and ketones. Also, metallacyclobutenes such as **3** and **10** promise to exhibit rich M-C and perhaps M-O(S) insertion chemistry (as do their nitrogen-containing analogues),[13] and experiments designed to test this expectation will be reported in due course.

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Supplementary Material Available: Spectroscopic and analytical data for complexes **2-10c** and details of the structure determinations for **9a** and **10b** including experimental descriptions, ORTEP drawings showing full atomic numbering, crystal and data collection parameters, general temperature factor expressions (B's), positional parameters and their estimated standard deviations, and intramolecular distances and angles (30 pages); listing of observed and calculated structure factors for **9a** and **10b** (34 pages). Ordering information is given on any current masthead page.

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[13] Baranger, A. M.; Walsh, P. J.; Bergman, R. G., results to be published.

Sugars as DNA Binders: A Comment on the Calicheamicin Oligosaccharide

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Preorganization is one of the first principles of tight binding.[1] In general, the more the conformation of a free ligand resembles its bound conformation, the better it binds. Small molecules that bind in the minor groove of DNA tend to be extended structures that present an essentially acyclic array of functionality to the groove and nature uses a variety of strategies to rigidify these molecules.[2,3] The recent discovery of calicheamicin γ^1, a small antitumor antibiotic that cleaves DNA site specifically, has drawn attention to the important role that oligosaccharides may play in DNA binding.[4] Oligosaccharides are components of many natural DNA binders, but their contributions to the energetics and specificity of binding are only beginning to be explored.[5] Below we report the results of NMR studies on the oligosaccharide portion of calicheamicin. We suggest that oligosaccharides may be well suited to function as minor groove binders because they are substantially preorganized. Some of the unusual structural features of calicheamicin are discussed in relation to their possible role in DNA binding.

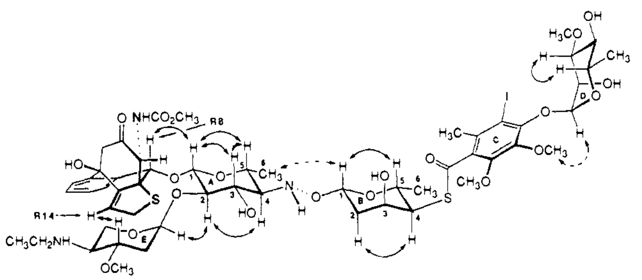

Figure 1. Calicheamicin ϵ. Selected through-space connectivities are indicated by bold (strong NOEs) or dashed (weak NOEs) arrows. ROESY experiments were carried out with 200-300-ms mixing times and an approximately 3-KHz spin-lock field.

NMR studies of calicheamicin ϵ (Figure 1), the rearrangement product of γ^1,[6] were carried out in CD_3OD, $CDCl_3$, and DMSO-d_6, three solvents that differ greatly in their hydrogen-bonding capabilities and dielectric constants. Double-quantum-filtered COSY was used to assign chemical shifts, and rotating frame nuclear Overhauser enhancement spectroscopy (ROESY)[7] was used to determine through-space connectivities (a table of ^{1}H NMR chemical shifts, J coupling constants, and NOEs for the oligosaccharide portion of calicheamicin ϵ is provided as supplementary material). The coupling constants and intraresidue NOEs of three of the sugar rings are virtually identical in all three solvents and are consistent with a single chair conformer for each monosaccharide: $^4C_1$ for the A and B rings and $^1C_4$ for the D ring. Temperature experiments conducted in CD_3OD and $CDCl_3$ indicate that neither the coupling constants nor the chemical shifts of the three sugars change significantly from -50 to +50 °C. Taken together, these results imply that there is a large free energy difference between the lowest energy ring conformers and all others. Conformational rigidity is a general feature of substituted six-membered rings and may make them ideal building blocks for DNA binders. While no experimental information about the bound conformation of the calicheamicin oligosaccharide has been obtained yet, it is clear that the energy cost of significantly distorting the A, B, or D rings upon binding would be substantial.[8]

The room-temperature coupling constants and NOEs of the remaining sugar, the E ring, are consistent with a chair conformation with an axial glycosidic linkage. However, the H1-H2e couplings differ notably in $CDCl_3$ and the more polar solvents,[9] suggesting that there is a degree of conformational flexibility in the E ring. Consistent with this interpretation, the E-ring resonances broaden and shift significantly below 0 °C in CD_3OD.

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[2] Both fused and unfused aromatic rings are common in small molecules that bind to DNA. In netropsin, distamycin, and related molecules, amide bonds, which have high rotational barriers and single preferred (trans) conformations, join sequential aromatic rings. (a) For a review of minor groove binders, see: Zimmer, C.; Wahnert, U. *Prog. Biophys. Mol. Biol.* **1986**, *47*, 31. (b) Dervan, P. B. *Science* **1986**, *232*, 464. (c) Sigman, D. S. *Acc. Chem. Res.* **1986**, *19*, 180.

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[6] NMR studies on calicheamicin γ^1 were carried out in CD_3OD and the oligosaccharide conformation appeared to be identical with that in calicheamicin ϵ.

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[8] In view of these results it is unlikely that the A ring exists in a boat conformation as depicted in ref 5c. Professor Schreiber has reached a similar conclusion (private communication).

[9] ^{1}H NMR ($CDCl_3$) H1 (d, J = 3 Hz); (CD_3OD, DMSO) H1 (t, J = 3 Hz).