

of binding, and the extent to which the latter are associated with the carbohydrate side chain or the enediyne,²¹ will emerge in further experiments.

Acknowledgment. We are pleased to acknowledge stimulating discussions over several years on the mechanism of calicheamicin action with Drs. G. A. Ellestad, D. B. Borders, and M. D. Lee (Lederle Laboratories). We are deeply grateful to Lever Brothers (J.J.H.) and The Royal Commission for The Exhibition of 1851 and the Dimitri V. d'Arbeloff Fund (J.J.DeV.) for fellowship support.

Supplementary Material Available: Partial ¹H NMR spectra for **2** and **5** and homonuclear decoupling of H-8 in **2** (1 page). Ordering information is given on any current masthead page.

(21) Experiments conducted with the esperamicin series suggest that while the various carbohydrate segments confer differing affinities to DNA, it is the enediyne portion that appears principally responsible for the sequence specificity of the DNA cleavages exhibited by this class of antibiotics.⁴

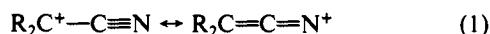
1-Cyano- and 2-Cyano-2-bicyclo[2.1.1]hexyl Cations

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Over the past decade, electron-deficient carbocations have been studied extensively.^{1,2} Both α - and β -cyano-substituted cations form at greatly reduced rates relative to their H analogues. A β -cyano group is more rate retarding ($k_H/k_{\beta-CN} = 10^5$ – 10^7)^{3,4} than an α -cyano group ($k_H/k_{\alpha-CN} = 10^3$ – 10^4).^{4,5} Since α -cyano groups appear to be less cation destabilizing than would be expected on the basis of a purely inductive effect, resonance stabilization has been invoked (eq 1).^{5–8} Partial nitrenium character is also indicated by the ¹³C and ¹⁵N NMR spectra of α -cyano carbocations (R = Ar).⁹



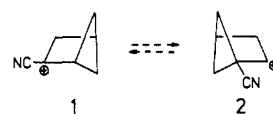
Product studies are less definitive. Many α -cyano substrates prefer elimination to substitution.^{4,5} Others rearrange with predominant formation of β -cyano products,^{3,10} derived from the allegedly less stable cations. In an effort to resolve these inconsistencies, and to adduce stereochemical evidence, we report here on the 2- and 1-cyano-2-bicyclo[2.1.1]hexyl cations (**1** and **2**). Our experience with the parent ion¹¹ suggested that elimination

Table I. Solvolysis Rate Constants of **3** and **4**

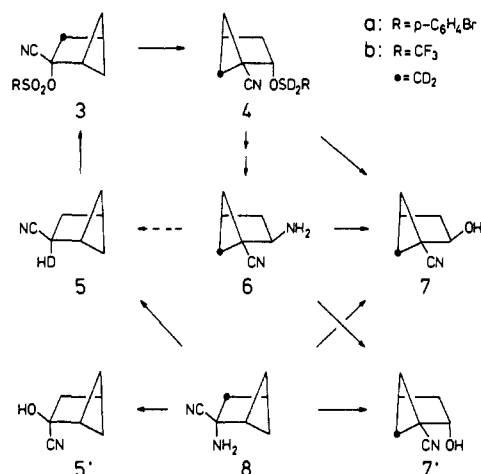
substrate, conditns	$k \times 10^4$ (s ⁻¹)	rel rates
2-bicyclo[2.1.1]hexyl brosylate, 80% EtOH, 75 °C ^a	73	1.6 · 10 ³
3a , 80% EtOH, 75 °C	0.048 ± 0.003	1
3b , 80% EtOH, 0 °C	3.2 ± 0.5	
3b , dioxane-H ₂ O (1:1), 0 °C	4.6 ± 0.7	2.6 × 10 ²
4b , dioxane-H ₂ O (1:1), 29.9 °C	0.87 ± 0.01	
4b , dioxane-H ₂ O (1:1), 34.8 °C	1.66 ± 0.02	
4b , dioxane-H ₂ O (1:1), 41.9 °C	3.63 ± 0.05	
4b , dioxane-H ₂ O (1:1), 50.2 °C	8.91 ± 0.13	
4b , dioxane-H ₂ O (1:1), 0 °C ^b	0.018	1

^a Bentley, T. W.; Goer, B.; Kirmse, W. *J. Org. Chem.* **1988**, *53*, 3066. The titrimetric rate constant is not corrected for internal return (62% in dioxane-H₂O¹¹). ^b Extrapolated from other temperatures.

would not occur, and interconversion of **1** and **2** by Wagner-Meerwein rearrangement would directly attest to the relative stabilities. We find that the α -cyano cation **1** is less stable than the β -cyano cation **2**. The solvolysis rates of the triflates **3b** and **4b** do not reflect the relative stabilities of the cations, due to large counteracting ground-state effects.



Bicyclo[2.1.1]hexan-2-one¹² was converted to the cyanohydrin **5** by standard procedures¹³ (Me₃SiCN/ZnI₂ followed by 3 N HCl; 86%). Brosylation of the cyanohydrin (BsCl/Py, 0 → 20 °C, 6 days, 84%) afforded **3a**. In 80% EtOH at 75 °C, **3a** rearranged slowly to give 1-cyano-2-bicyclo[2.1.1]hexyl brosylate (**4a**), which proved to be extremely unreactive. Brosylate **3a**, containing 47% alkoxy-¹⁸O, was rearranged to give **4a** with 36% alkoxy-¹⁸O, i.e., with partial redistribution of ¹⁸O to the sulfonyl group.¹⁴ These data indicate that ionization of **3a** leads to tight ion pairs which recombine with exclusive formation of **4a**. The rate of the rearrangement, **3a** → **4a**, was found to be slower than the solvolysis rate of 2-bicyclo[2.1.1]hexyl brosylate by a factor of 2 × 10³ (Table I), in good agreement with previous results for α -cyano sulfonates.^{4,5}



For a comparison of α - and β -cyano substrates, we prepared the triflate **3b** from the cyanohydrin (Tf₂O/Py, 0 °C, 2 h, 75%). Dilute solutions of **3b** in nonpolar solvents were stable for several days. In polar solvents, **3b** rearranged rapidly and quantitatively with formation of the 1-cyano isomer **4b**.¹⁵ The enthalpy of the

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(14) Internal return of sulfonates with incomplete scrambling of ¹⁸O is common; see: Goering, H. L.; Jones, B. E. *J. Am. Chem. Soc.* **1980**, *102*, 1628 and references cited therein.

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rearrangement, $\Delta H_f(25^\circ\text{C}) = -9.6 \pm 1$ kcal/mol, was determined calorimetrically.¹⁶ The data reveal a large difference in ΔH_f° , favoring **4b**. The underlying effects are addressed in an accompanying paper.¹⁸

Even in aqueous dioxane and in formic acid, **3b** reacted to give $\geq 95\%$ of **4b** and $\leq 5\%$ of solvolysis products.¹⁹ The rearrangement of [3,3-²H]-**3b** afforded $\geq 95\%$ of [5,5-²H₂]-**4b**, i.e., the triflate counterion returns to the same side of the molecular plane from which it departed. At elevated temperatures, **4b** solvolyzed with complete ($\pm 5\%$) inversion, giving rise to [6,6-²H₂]-**7**. Nucleophilic attack at the covalent substrate is most likely since no redistribution of alkoxy.¹⁸ **O** was detected in the triflate **4b** that was recovered after 50–75% conversion. The **3b**:**4b** rate ratio (Table I) and the derived ratio $k_H/k_{\beta\text{-CN}} = 4 \times 10^5$ conform with previous work,³⁻⁵ although the ionization of **3b** proceeds only to tight ion pairs, and **4b** does not ionize at all.

In order to generate the cations **1** and **2**, we resorted to diazotization. A modified Strecker synthesis (KCN/NH₄Cl/H₂O/MeOH, 80 °C, 16 h, 41%) converted bicyclo[2.1.1]hexan-2-one to the amino nitrile **8**, which was partially resolved (20% ee) by HPLC of the (*S*)-2-acetoxypyrrolidine.²⁰ Diazotization of optically active **8** (NaNO₂, dilute HClO₄, pH 3.5) produced the alcohols **7** and **5** (81:19) as racemates ($0 \pm 2\%$ ee). Moreover, [3,3-²H]-**8** gave **7** with random distribution of the deuterium between positions **5** and **6** ($7:7' = 1.00 \pm 0.05$). The amino nitrile [6,6-²H₂]-**6** was prepared from [5,5-²H₂]-**4** by displacement with lithium azide (tetraglyme, 60 °C, 20 h, 61%), followed by catalytic hydrogenation (Pd-C, ether, 92%). Diazotization of [6,6-²H₂]-**6** afforded **7** with a 3:1 distribution of the deuterium between positions **5** and **6**; the product ratio **7**:**5** was 98.5:1.5.

The stereorandom reactions of **8** point to the achiral carbocations **1** and **2** as intermediates. Only 50% of the diazonium ions derived from **6** follow a stereorandom path (k_c), yielding **7** + **7'** and **5** in a 97:3 ratio; the remaining 50% undergo inverting displacement (k_i), leading to **7'**. With the reasonable assumption that capture of the intervening carbocations is diffusion-controlled, the rearrangement **1** → **2** is found to be exothermic by 2–3 kcal/mol.

Two major conclusions may be drawn from our results: (i) The stereoselectivity of the parent 2-bicyclo[2.1.1]hexyl cation, attributed to bridging (σ delocalization),¹¹ is completely lost on cyano substitution. In spite of enhanced electron demand, the intermediates **1** and **2** behave as classical ions whose interconversion competes with solvent capture. (ii) In contrast to current views, the β -cyano cation **2** is more stable than the α -cyano cation **1** by 2–3 kcal/mol. The order of stabilities suggests that charge delocalization (eq 1) may not be as important as previously thought. The energy difference of the triflate precursors (9–10 kcal/mol) exceeds that of the cations. This explains why the less stable ion **1** is formed more readily, in violation of well-established rules for hydrocarbon ions.²¹

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(15) The rearrangement **3b** → **4b** was associated with partial scrambling of alkoxy.¹⁸ **O** (45% in **3b** → 34% in **4b**), in close agreement with the behavior of **3a**.

(16) Solutions of **3b** in diisopropyl ether were added to nitromethane. The heat evolved was measured in a microcalorimeter¹⁷ and corrected for the heat of mixing and the heat of solution of **4b**, determined in separate experiments.

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(18) Wu, Y.-D.; Kirmse, W.; Houk, K. N. *J. Am. Chem. Soc.*, following paper in this issue.

(19) Similar behavior has been reported for 2-(methoxycarbonyl)-2-bicyclo[2.1.1]hexyl mesylate: Della, E. W.; Eley, G. M.; Skouroumounis, G. *Tetrahedron Lett.* **1986**, *27*, 5993.

(20) The diastereomeric (*S*)-2-acetoxypyrrolidine derivatives of **5**, **7**, and **8** were cleanly separated by GC on capillary columns (providing estimates of the ee) whereas the diastereomeric amides overlapped on HPLC (silica gel, ether-hexane, 7:3). Hydrolysis (2 N HCl, 60 °C, 3 h) of enriched amide fractions provided optically active **8** of unknown configuration.

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Registry No. (\pm)-[3,3-²H₂]-**3a**, 126823-31-2; (\pm)-**3b**, 126823-32-3; (\pm)-[3,3-²H₂]-**3b**, 126823-35-6; (\pm)-**4a**, 126823-34-5; (\pm)-[5,5-²H₂]-**4a**, 126823-42-5; (\pm)-**4b**, 126823-33-4; (\pm)-[5,5-²H₂]-**4b**, 126823-36-7; (\pm)-**5'**, 126823-39-0; (\pm)-[6,6-²H₂]-**6**, 126823-41-4; (\pm)-**7'**, 126823-38-9; (\pm)-**8**, 126823-37-8; (\pm)-[3,3-²H₂]-**8**, 126823-40-3; bicyclo[2.1.1]hexan-2-one, 5164-64-7.

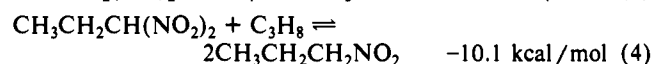
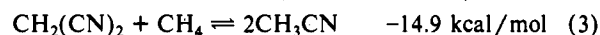
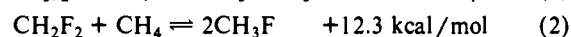
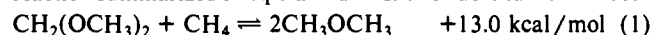
Geminal Group Interactions

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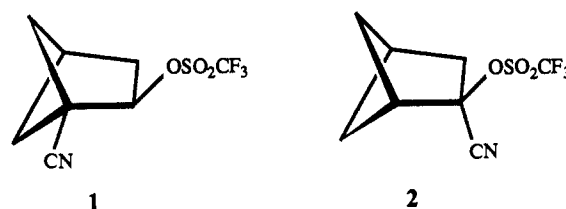
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When two functional groups are attached to the same atom, they can interact with each other to cause either stabilization or destabilization. This is the geminal effect.¹⁻⁴ If two substituents are both strong σ -acceptors and strong π -donors, there is a strongly stabilizing interaction, as indicated by the experimental heats of reaction summarized in eq 1 and 2.⁵ If two substituents are both



σ - and π -acceptors, there is strong destabilization, as shown by eqs 3 and 4.⁶ If one of the substituents is a strong acceptor and the other is a σ -acceptor but π -donor (OR, F, etc.), the two effects may compete.

In an investigation of the influence of cyano groups on cation stabilities, Kirmse and Goer determined that compound **1**, which has 1,2-disubstitution, is about 10 kcal/mol more stable than its isomer **2**, which has CN and OSO₂CF₃ (OTf) groups attached to the same carbon.⁷ There could be two possible reasons for the relative stability of **1**. One is that the CN group is attached to a tertiary carbon in **1**, and this may have some special stabilizing effect; the other is that CN and OTf are both electron-withdrawing, and 1,1-disubstitution in **2** might be particularly destabilizing.



The observation is of more general significance, since the relative stabilities may influence the interpretation of substituent effects upon stabilities of reactive intermediates. In the current case, the solvolyses of **1** and **2** lead to cations substituted by cyano groups.

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