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 ^{1}H 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

Wolfgang Kirmse* and Bernhard Goer

Fakultät für Chemie der Ruhr-Universität
D-4630 Bochum, Federal Republic of Germany

Received January 11, 1990

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 ($k_H/k_{\beta\text{-CN}} = 10^5$–$10^7$)[3,4] than an α-cyano group ($k_H/k_{\alpha\text{-CN}} = 10^3$–$10^4$).[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 ^{13}C and ^{15}N NMR spectra of α-cyano carbocations (R = Ar).[9]

$$R_2C^+{-}C{\equiv}N \leftrightarrow R_2C{=}C{=}N^+ \qquad (1)$$

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 ion[11] suggested that elimination 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.

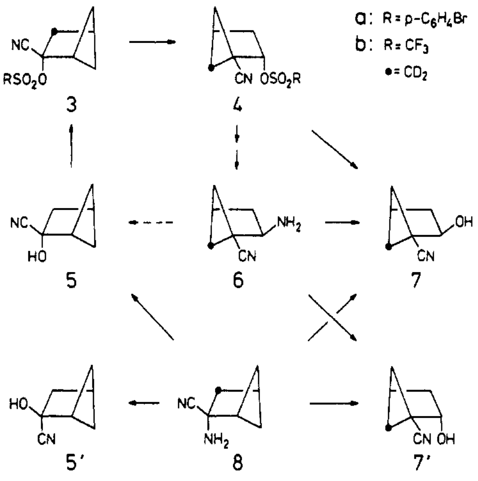
Table I. Solvolysis Rate Constants of **3** and **4**

substrate, conditns	$k \times 10^4$ (s^{-1})	rel rates
2-bicyclo[2.1.1]hexyl brosylate, 80% EtOH, 75 °C[a]	73	$1.6 \cdot 10^3$
3a, 80% EtOH, 75 °C	0.048 ± 0.003	1
3b, 80% EtOH, 0 °C	3.2 ± 0.5	
3b, dioxane–H_2O (1:1), 0 °C	4.6 ± 0.7	2.6×10^2
4b, dioxane–H_2O (1:1), 29.9 °C	0.87 ± 0.01	
4b, dioxane–H_2O (1:1), 34.8 °C	1.66 ± 0.02	
4b, dioxane–H_2O (1:1), 41.9 °C	3.63 ± 0.05	
4b, dioxane–H_2O (1:1), 50.2 °C	8.91 ± 0.13	
4b, dioxane–H_2O (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–H_2O[11]). [b] Extrapolated from other temperatures.

1 2

Bicyclo[2.1.1]hexan-2-one[12] was converted to the cyanohydrin **5** by standard procedures[13] (Me_3SiCN/ZnI_2 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-^{18}O, was rearranged to give **4a** with 36% alkoxy-^{18}O, i.e., with partial redistribution of ^{18}O 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 2×10^3 (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 (Tf_2O/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

---

[1] For reviews, see: (a) Gassman, P. G.; Tidwell, T. T. *Acc. Chem. Res.* **1983**, *16*, 279. (b) Tidwell, T. T. *Angew. Chem.* **1984**, *96*, 16; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 20.

[2] For a comprehensive list of references, see: Creary, X.; Mehrsheikh-Mohammadi, M. E.; Eggers, M. D. *J. Am. Chem. Soc.* **1987**, *109*, 2435.

[3] Gassman, P. G.; Saito, K.; Talley, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 7613.

[4] Gassman, P. G.; Saito, K. *Tetrahedron Lett.* **1981**, 1311.

[5] Gassman, P. G.; Talley, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 1214.

[6] Dixon, D. A.; Charlier, P. A.; Gassman, P. G. *J. Am. Chem. Soc.* **1980**, *102*, 3957.

[7] Paddon-Row, M. N.; Santiago, C.; Houk, K. N. *J. Am. Chem. Soc.* **1980**, *102*, 6561.

[8] Dixon, D. A.; Eades, R. A.; Frey, R.; Gassman, P. G.; Hendewerk, M. L.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 3885.

[9] (a) Olah, G. A.; Prakash, G. K. S.; Arvanaghi, M. *J. Am. Chem. Soc.* **1980**, *102*, 6640. (b) Olah, G. A.; Arvanaghi, M.; Prakash, G. K. S. *Ibid.* **1982**, *104*, 1628. (c) Krishnamurthy, V. A.; Prakash, G. K. S.; Iyer, P. S.; Olah, G. A. *Ibid.* **1986**, *108*, 1575.

[10] Gassman, P. G.; Talley, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 4138.

[11] Kirmse, W.; Zellmer, V.; Goer, B. *J. Am. Chem. Soc.* **1986**, *108*, 4912.

[12] Bond, F. T.; Jones, H. L.; Scerbo, I. *Tetrahedron Lett.* **1965**, 4685. Bond, F. T.; Jones, H. L.; Scerbo, I. *Photochem. Synth.* **1971**, *1*, 33.

[13] Gassman, P. G.; Talley, J. J. *Tetrahedron Lett.* **1978**, 3773.

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

0002-7863/90/1512-4556$02.50/0 © 1990 American Chemical Society

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

Even in aqueous dioxane and in formic acid, **3b** reacted to give ≥95% of **4b** and ≤5% of solvolysis products.[19] The rearrangement of [3,3-^{2}H]-**3b** afforded ≥95% of [5,5-$^2H_2$]-**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 (±5%) inversion, giving rise to [6,6-$^2H_2$]-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 dediazoniation. A modified Strecker synthesis ($KCN/NH_4Cl/H_2O$/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-acetoxypropionamide.[20] Diazotization of optically active **8** ($NaNO_2$, dilute $HClO_4$, pH 3.5) produced the alcohols **7** and **5** (81:19) as racemates (0 ± 2% ee). Moreover, [3,3-^{2}H]-**8** gave **7** with random distribution of the deuterium between positions 5 and 6 (**7**:**7′** = 1.00 ± 0.05). The amino nitrile [6,6-$^2H_2$]-**6** was prepared from [5,5-$^2H_2$]-**4** by displacement with lithium azide (tetraglyme, 60 °C, 20 h, 61%), followed by catalytic hydrogenation (Pd–C, ether, 92%). Diazotization of [6,6-$^2H_2$]-**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_s), leading to **7′**. With the resonable 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]

Acknowledgment. We are indebted to Professor W. R. Roth and Dr. H. W. Lennartz for the calorimetric measurements and to Professor H. Günther for some of the ^{2}H NMR spectra. Financial support from the Fonds der Chemischen Industrie is gratefully acknowledged.

Registry No. (±)-[3,3-$^2H_2$]-**3a**, 126823-31-2; (±)-**3b**, 126823-32-3; (±)-[3,3-$^2H_2$]-**3b**, 126823-35-6; (±)-**4a**, 126823-34-5; (±)-[5,5-$^2H_2$]-**4a**, 126823-42-5; (±)-**4b**, 126823-33-4; (±)-[5,5-$^2H_2$]-**4b**, 126823-36-7; (±)-**5′**, 126823-39-0; (±)-[6,6-$^2H_2$]-**6**, 126823-41-4; (±)-**7′**, 126823-38-9; (±)-**8**, 126823-37-8; (±)-[3,3-$^2H_2$]-**8**, 126823-40-3; bicyclo[2.1.1]hexan-2-one, 5164-64-7.

---

(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 microcalorimeter[17] and corrected for the heat of mixing and the heat of solution of **4b**, determined in separate experiments.

(17) Roth, W. R.; Lennartz, H. W. *Chem. Ber.* **1980**, *113*, 1806.

(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.; Elsey, G. M.; Skouroumounis, G. *Tetrahedron Lett.* **1986**, *27*, 5993.

(20) The diastereomeric (*S*)-2-acetoxypropionyl 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.

(21) (a) Arnett, E. M.; Petro, C. *J. Am. Chem. Soc.* **1978**, *100*, 5408. (b) Arnett, E. M.; Petro, C.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1979**, *101*, 522.

Geminal Group Interactions

Yun-Dong Wu,[†] W. Kirmse,[‡] and K. N. Houk*,[†]

Department of Chemistry and Biochemistry
University of California, Los Angeles
Los Angeles, California 90024
Fakultät für Chemie der Ruhr-Universität
D-4630 Bochum, Federal Republic of Germany

Received January 11, 1990

When two functional groups are attached to the same atom, they can interact with each other to cause either stabilization or destablization. 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

$$CH_2(OCH_3)_2 + CH_4 \rightleftharpoons 2CH_3OCH_3 \qquad +13.0\ \text{kcal/mol} \quad (1)$$

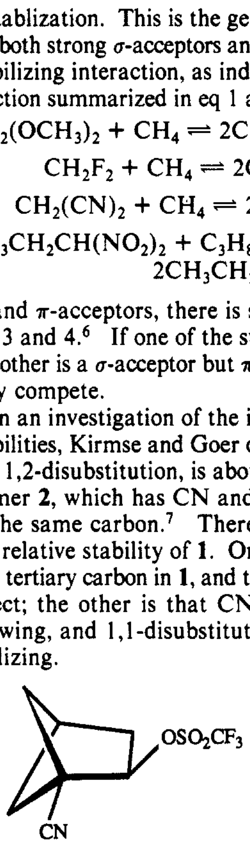
$$CH_2F_2 + CH_4 \rightleftharpoons 2CH_3F \qquad +12.3\ \text{kcal/mol} \quad (2)$$

$$CH_2(CN)_2 + CH_4 \rightleftharpoons 2CH_3CN \qquad -14.9\ \text{kcal/mol} \quad (3)$$

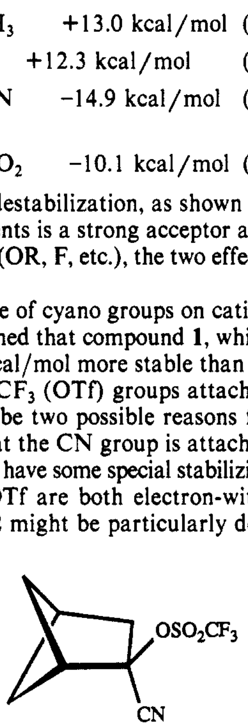
$$CH_3CH_2CH(NO_2)_2 + C_3H_8 \rightleftharpoons 2CH_3CH_2CH_2NO_2 \qquad -10.1\ \text{kcal/mol} \quad (4)$$

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 OSO_2CF_3 (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 destablizing.



1



2

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.

[†] University of California, Los Angeles.

[‡] Fakultät für Chemie der Ruhr-Universität.

(1) For a general review, see: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab. Initio Molecular Theory*; Wiley: New York, 1986, p 356 ff.

(2) Leroy, G. *J. Mol. Struct.* **1985**, *120*, 91 and references cited therein.

(3) Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467.

(4) Benson, S. W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 812.

(5) Schleyer, P. v. R.; Kos, A. J. *Tetrahedron* **1983**, *39*, 1141. Schleyer, P. v. R.; Jemmis, E. D.; Spitznagel, G. W. *J. Am. Chem. Soc.* **1985**, *107*, 6393. Reed, A. R.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1987**, *109*, 7362 and references cited therein.

(6) Based on experimental enthalpies of formation, $\Delta H_f°$(gas), taken from the following: Pedley, J. B.; Naylor, R. D.; Kirby, S. P. *Thermochemical Data of Organic Compounds*; Champan and Hall: London, 1986.

(7) Kirmse, W.; Goer, B. *J. Am. Chem. Soc.*, preceding paper in this issue.

0002-7863/90/1512-4557$02.50/0