aza-Cope–Mannich reaction for stereocontrolled alkaloid construction.

Acknowledgment. Support of this research by a Javits Neuroscience Investigator Award (NS-12389) is gratefully acknowledged. NMR and mass spectra were determined at UCI with spectrometers acquired with the assistance of NSF Shared Instrumentation Grants. We particularly thank Dr. Henry M. Fales (NIH) for a sample of natural pancracine.

Marked Leaving Group Strain in (*Z*)-2-Ethylidenebicyclo[2.2.2]oct-1-yl Triflate and Its Significant Relief in (*Z*)-2-Ethylidenebicyclo[3.2.2]non-1-yl Mesylate

Ken'ichi Takeuchi,* Yasushi Ohga, and Toshikazu Kitagawa

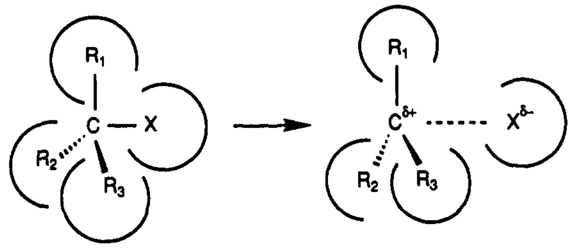
Department of Hydrocarbon Chemistry, Faculty of Engineering, Kyoto University, Sakyo-ku, Kyoto 606, Japan

Received April 22, 1991

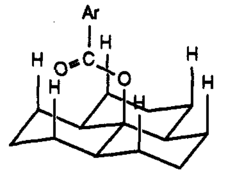
Summary: The rate of ethanolysis at 25 °C of (*Z*)-2-ethylidenebicyclo[2.2.2]oct-1-yl triflate [(*Z*)-**3**] is 217 times faster than that of its *E* isomer, whereas more flexible (*Z*)-2-ethylidenebicyclo[3.2.2]non-1-yl mesylate solvolyzes 3.4 times slower than its *E* isomer, indicating marked leaving-group strain in the ground state of (*Z*)-**3**, which is supported by MM2 calculations.

In the ionization of a crowded molecule $(R)_3CX$, both the back strain (B-strain) among the three alkyl groups and the front strain (F-strain) between the leaving group X and the alkyl groups are relieved, resulting in enhancement of solvolysis rates (Scheme I).[1,2] These phenomena have constituted one of the major subjects in computational chemistry.[2,3]

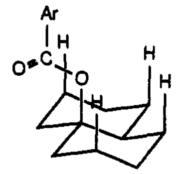
Scheme I



In principle, when the R groups are made bulkier, not only B-strain but also F-strain increases.[2f] Moreover, ionization may well cause an increase in strain between alkyl groups resulting from shortening of the C^+–C bond in the carbocation.[2j,4] Therefore, the rate enhancement solely due to F-strain is generally difficult to realize. Changing the size of the leaving group X in $(R)_3CX$ with varying sizes of the R group achieved considerable success.[2b,h,i] However, concomitant differential change in solvation should always be taken into account.[2g,5] Previously, the tosylate leaving group was suggested to cause greater F-strain than the bromide in bridgehead derivatives,[6] but this was questioned by recent calculations.[3a] The most straightforward approach would be to design a system that shows a dramatic reactivity change upon minimum structural modification with the B-strain and the leaving group being unchanged. In this context, the most unambiguous case reported so far would be the finding that *trans,trans,trans*-perhydro-9b-phenalyl *p*-nitrobenzoate (**1**-OPNB) solvolyzes 2860 times faster than *trans*-9-decalyl *p*-nitrobenzoate (**2**-OPNB) in 80% acetone at 25 °C.[2c] Since the rate enhancement essentially vanishes in the chloride **1**-Cl, the major F-strain in **1**-OPNB has been postulated to exist between the carbonyl group (and/or the aryl group) and the ring system.[2c,3c]



1-OPNB



2-OPNB

We now report another clear-cut example. The structural modification employed in the present study is much simpler than annulation of **2**-OPNB leading to **1**-OPNB. We compared the rates of ethanolysis between (*Z*)-2-ethylidenebicyclo[2.2.2]oct-1-yl triflate [(*Z*)-**3**], the *E* isomer [(*E*)-**3**], and the 2-methylene homologue **4**.[7] For a comparison, (*Z*)- and (*E*)-2-ethylidenebicyclo[3.2.2]non-1-yl

---

[1] For reviews, see: (a) Tidwell, T. T. *Tetrahedron* 1978, *34*, 1855. (b) Stirling, C. J. M. *Tetrahedron* 1985, *41*, 1613.

[2] (a) Brown, H. C.; Fletcher, R. S. *J. Am. Chem. Soc.* 1949, *71*, 1845. (b) Brown, H. C.; Stern, A. *J. Am. Chem. Soc.* 1950, *72*, 5068. (c) Slutsky, J.; Bingham, R. C.; Schleyer, P. v. R.; Dickason, W. C.; Brown, H. C. *J. Am. Chem. Soc.* 1974, *96*, 1969. (d) Bartlett, P. D.; Tidwell, T. T. *J. Am. Chem. Soc.* 1955, *77*, 2806. (e) Bartlett, P. D.; Tidwell, T. T. *J. Am. Chem. Soc.* 1968, *90*, 4421. (f) Cheng, P.-T.; Nyburg, S. C.; Thankachan, C.; Tidwell, T. T. *Angew. Chem., Int. Ed. Engl.* 1977, *16*, 654. (g) Lomas, J. S.; Sagatys, D. S.; Dubois, J.-E. *Tetrahedron Lett.* 1973, 1791. (h) Lomas, J. S.; Luong, P. K.; Dubois, J.-E. *J. Am. Chem. Soc.* 1977, *99*, 5478. (i) Lomas, J. S.; Luong, P. K.; Dubois, J.-E. *J. Org. Chem.* 1979, *44*, 1647. (j) Lomas, J. S. *Nouv. J. Chim.* 1984, *8*, 365. (k) Sliwinski, W. F.; Su, T. M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* 1972, *94*, 133. (l) Fry, J. L.; Engler, E. M.; Schleyer, P. v. R. *J. Am. Chem. Soc.* 1972, *94*, 4628. (m) Faulkner, D.; McKervey, M. A.; Lenoir, D.; Senkler, C. A.; Schleyer, P. v. R. *Tetrahedron Lett.* 1973, 705. (n) Farcasiu, D. *J. Org. Chem.* 1978, *43*, 3878. (o) Lenoir, D.; Frank, R. M. *Chem. Ber.* 1981, *114*, 3336.

[3] (a) Müller, P.; Blanc, J.; Mareda, J. *Helv. Chim. Acta* 1986, *69*, 635. (b) Müller, P.; Mareda, J. *Helv. Chim. Acta* 1987, *70*, 1017. (c) Müller, P.; Blanc, J.; Mareda, J. *Chimia* 1987, *41*, 399.

[4] Olah, G. A.; Prakash, G. K. S.; Krishnamurti, R. *J. Am. Chem. Soc.* 1990, *112*, 6422.

[5] Tidwell, T. T. *J. Org. Chem.* 1974, *39*, 3533.

[6] Bingham, R. C.; Schleyer, P. v. R. *J. Am. Chem. Soc.* 1971, *93*, 3189.

[7] The new substrates (*Z*)-**3**, (*E*)-**3**, (*Z*)-**5**, and (*E*)-**5** were prepared as follows. A Wittig ethylidenation[8] of the *tert*-butyldimethylsilyl (BDMS) ether of 1-hydroxybicyclo[2.2.2]octan-2-one[9] afforded solely (*Z*)-**3**-OBDMS as an oil in 85% yield, which on olefin inversion by the phosphorus betaine method[10] gave (*E*)-**3**-OBDMS as an oil in 69% yield. In a similar Wittig ethylidenation of the BDMS ether of 1-hydroxybicyclo[3.2.2]nonan-2-one[9,11] were isolated (*Z*)-**4**-OBDMS and (*E*)-**4**-OBDMS in 16% and 22% yields, respectively. The *Z* and *E* configurations were based on ^1H NMR NOE difference experiments: on irradiation of the olefinic proton, *Z* isomers showed NOEs on both the methyl and C(3) protons, whereas *E* isomers showed NOEs on only the methyl protons. The BDMS ethers were desilylated by treatment with tetrabutylammonium fluoride in THF and then converted to triflates or mesylates. The only impurity was the corresponding alcohol. The 2-methylene homolgoues **4** and **6** were described previously.[9]

[8] Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* 1963, *28*, 1128.

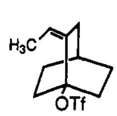
0022-3263/91/1956-5007$02.50/0

Table I. Rate Data of Ethanolysis of 2-Ethylidene or 2-Methylene Bicyclic Bridgehead Compounds[a]

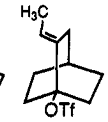
compd[b]	temp, °C	k, s^{-1}	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	rel rates at 25 °C	
(*Z*)-**3**[c]	25.0	4.04×10^{-4}[d]	23.8	5.6	1365	217
	40.0	2.89×10^{-3}[d]				
(*E*)-**3**[c]	25.0	1.86×10^{-6}[e]	26.8	5.1	6.3	1
	50.0	6.65×10^{-5}[e]				
4[g]	25.0	2.96×10^{-7}[f,g]	27.1	2.3	1	
	50.0	1.09×10^{-5}[e,g]				
	75.0	2.40×10^{-4}[e,g]				
(*Z*)-**5**[c]	25.0	5.49×10^{-4}[d]	23.2	4.3	77	0.30
	40.0	3.76×10^{-3}[d]				
(*E*)-**5**[c]	25.0	1.86×10^{-3}[d]	21.6	1.3	259	1
	40.0	1.11×10^{-2}[d]				
6[g]	25.0	7.17×10^{-6}[e,g]	24.3	−0.4	1	
	50.0	1.86×10^{-4}[e,g]				

[a] In the presence of 0.025 M 2,6-lutidine. [b] All new compounds showed spectral data consistent with the proposed structures. [c] Oil. [d] Determined conductimetrically. [e] Determined titrimetrically. [f] Extrapolated from data at other temperatures. [g] Reference 9.

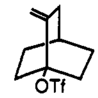
mesylates and the 2-methylene homologue [(*Z*)-**5**, (*E*)-**5**, and **6**, respectively] were also subjected to rate studies.[7] All the substrates gave exclusively the corresponding bridgehead ethyl ethers. The ethanolysis rate data are summarized in Table I.



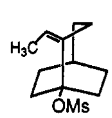
(Z)-**3**



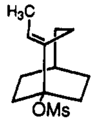
(E)-**3**



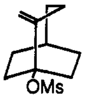
4



(Z)-**5**



(E)-**5**



6

The rate of ethanolysis of (*Z*)-2-ethylidenebicyclo[2.2.2]oct-1-yl triflate [(*Z*)-**3**] is 217 times faster than that of the *E* isomer [(*E*)-**3**] at 25 °C. In contrast, the more flexible substrate (*Z*)-2-ethylidenebicyclo[3.2.2]non-1-yl mesylate [(*Z*)-**5**] solvolyzes 3.4 times slower than the *E* isomer [(*E*)-**5**] in ethanol at 25 °C.

Previously, we reported that allylic conjugation is essentially prohibited in the incipient carbocation from 2-methylenebicyclo[2.2.2]oct-1-yl triflate (**4**) for geometric reasons.[9] We attribute a major part of the enhanced rate for (*Z*)-**3** as compared with (*E*)-**3** to the relief of F-strain between the (*Z*)-methyl substituent and the leaving group. Semiempirical molecular orbital calculations (AM1)[12] on bridgehead carbocations (*Z*)-$\mathbf{3}^+$ and (*E*)-$\mathbf{3}^+$ indicated that charge delocalization is similar in the two cations, being slightly smaller in the former: the net atomic charge on the cationic carbon is 0.403 for (*Z*)-$\mathbf{3}^+$ and 0.402 for (*E*)-$\mathbf{3}^+$. On the other hand, molecular mechanics calculations [MM2(87)][13] on bridgehead alcohols (*Z*)-**3**-OH and (*E*)-**3**-OH as surrogates for the triflates showed that the former is more strained than the latter by 2.5 kcal/mol. About 80% of this energy is explicable in terms of the sum of repulsion between the (*Z*)-methyl group and the oxygen atom and thereby induced deformation of the skeleton. Since the freely rotating CF_3SO_2 moiety is not expected to seriously interact with the (*Z*)-methyl group, the origin of the F-strain in (*Z*)-**3** is most probably attributed to the repulsion between the (*Z*)-methyl group and the ether oxygen atom on the bridgehead position. This presents a striking contrast to the previously reported system **1**-OPNB, where the ether oxygen atom is unimportant with respect to the F-strain.[2c]

In the more flexible 2-ethylidenebicyclo[3.2.2]non-1-yl system, the (*Z*)-**5**/(*E*)-**5** rate ratio is 0.30, which should be compared with the (*Z*)-**3**/(*E*)-**3** rate ratio of 217 for the rigid 2-ethylidenebicyclo[2.2.2]oct-1-yl system. This striking contrast reveals the importance of a rigid structure and coplanar arrangement of the methyl group and the reaction center for exerting the F-strain. Molecular mechanics calculations [MM2(87)][13] showed that (*Z*)-**5**-OH is slightly more strained than (*E*)-**5**-OH by only 0.3 kcal/mol. Apparently, F-strain is markedly reduced in (*Z*)-**5**. Interestingly, AM1 calculations[12] indicated that the positive charge of (*E*)-$\mathbf{5}^+$ is conjugatively more delocalized than that of (*Z*)-$\mathbf{5}^+$: the net atomic charge on the cationic carbon is 0.353 for (*E*)-$\mathbf{5}^+$ and 0.363 for (*Z*)-$\mathbf{5}^+$. This might be partly responsible for the faster rate for (*E*)-**5** than for (*Z*)-**5**. The much faster rates for (*Z*)-**5** and (*E*)-**5** than for **6** are explicable in terms of enhancement of allylic conjugation by the methyl substituent.[14]

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan, and a grant from the Asahi Glass Foundation.

Supplementary Material Available: ^{13}C NMR spectra for new substrates and ^{13}C NMR spectra, analytical data, and melting points for their precursor alcohols (9 pages). Ordering information is given on any current masthead page.

---

(9) Takeuchi, K.; Akiyama, F.; Ikai, K.; Shibata, T.; Kato, M. *Tetrahedron Lett.* **1988**, *29*, 873.

(10) Vedejs, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1973**, *95*, 822.

(11) Takeuchi, K.; Kitagawa, I.; Akiyama, F.; Shibata, T.; Kato, M.; Okamoto, K. *Synthesis* **1987**, 612.

(12) Calculated through the AMPAC system: QCPE 527.

(13) Obtained from QCPE.

(14) We have previously shown that the allylic conjugation is approximately 50% attained in the incipient carbocation from **6**.[9]