The Journal of
Organic
Chemistry

VOLUME 55, NUMBER 25 DECEMBER 7, 1990

Communications

Stability of 2-Oxo and 2-Methylene Bridgehead Carbocations in Solvolysis: Further Evidence for the Unimportance of π-Conjugative Stabilization in Tertiary α-Keto Cations

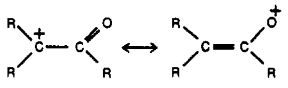
Ken'ichi Takeuchi,* Masayasu Yoshida, Yasushi Ohga, Akio Tsugeno, and Toshikazu Kitagawa

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

Received July 27, 1990

Summary: The solvolysis rate ratios of 2-methylene bicyclic bridgehead compounds relative to the parent compounds increase with flexibility of the ring system, whereas the corresponding rate ratios related to 2-oxo homologues are essentially constant, suggesting the unimportance of π-conjugative stabilization in tertiary α-keto cations.

In recent years, a number of solvolytic rate data have been interpreted to support the notion that the α-keto and α-cyano carbocations (**1** and **2**, respectively) are stabilized by π-conjugation to an extent which partly offsets the destabilizing inductive effect of the substituent.[1]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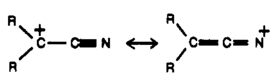
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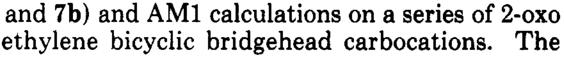
Very recently, Kirmse and his co-workers pointed out that the cyano group and the leaving group (-OSO_2R) attached to the same carbon atom interact with each other, resulting in significant destabilization (9–10 kcal/mol) of the ground state as compared with the β-cyano substrate.[2] This has been used to explain why the α-cyano carbocations **2** are relatively easily formed in solvolyses.[2a]

Previously, we have reported that the rates of solvolysis of 3,3-dimethyl-2-oxobicyclo[2.2.2]oct-1-yl triflate (**3a**) and 2-oxobicyclo[3.2.2]non-1-yl triflate (**5a**) relative to their corresponding parent compounds (**3c** and **5c**) are essentially identical ($10^{-8.4}$ for **3a**/**3c** and $10^{-8.3}$ for **5a**/**5c** in EtOH, 25 °C).[3] On the other hand, the rate ratio of the 2-methylene to the parent compound increases from $10^{-3.9}$ for **4b**/**4c** to $10^{-0.8}$ for **5b**/**5c**, indicating greater allylic conjugation in the ionization in **5b** than in **4b**.[3] Consequently, the essentially identical rate ratios for **3a**/**3c** and **5a**/**5c** have been interpreted to indicate the unimportance of π-conjugative stabilization of α-keto cations **1**.[3]



X=O	**3a**	(**4a**)	**5a**	**6a**	**7a**
X=CH_2	(**3b**)	**4b**	**5b**	**6b**	**7b**
X=H_2	**3c**	**4c**	**5c**	**6c**	**7c**

We now wish to report on the solvolyses of the bicyclo[3.3.1]non-1-yl and 3-homoadamantyl[4] systems containing a neighboring oxo or a methylene substituent (**6a**, **6b**, **7a**, and **7b**) and AM1 calculations on a series of 2-oxo or 2-methylene bicyclic bridgehead carbocations. The results further support the unimportance of π-conjugative stabilization of α-keto cation **1**.

The starting ketols for **6a** and **7a** prepared by the previously reported method[5] were converted to the triflates

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[1] (a) Gassman, P. G.; Tidwell, T. T. *Acc. Chem. Res.* **1983**, *16*, 279. (b) Tidwell, T. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 20. (c) Creary, X. *Acc. Chem. Res.* **1985**, *18*, 3. (d) Creary, X.; Hopkinson, A. C.; Lee-Ruff, E. In *Advances in Carbocation Chemistry*, Vol. 1; Creary, X., Ed.; Jai Press Inc.: Greenwich, CT, 1989; pp 45–92.

[2] (a) Kirmse, W.; Goer, B. *J. Am. Chem. Soc.* **1990**, *112*, 4556. (b) Wu, Y.-D.; Kirmse, W.; Houk, K. N. *Ibid.* **1990**, *112*, 4557.

[3] Takeuchi, K.; Akiyama, F.; Ikai, K.; Shibata, T.; Kato, M. *Tetrahedron Lett.* 1988, *29*, 873.

[4] A preliminary **7a**/**7c** rate ratio was $10^{-8.2}$: Takeuchi, K.; Kamata, J.; Shibata, T.; Okamoto, K. In *Studies in Organic Chemistry*, Vol. 31; Kobayashi, M., Ed.; Elsevier Science Publishers B. V.; Amsterdam, 1987; pp 303–310.

[5] (a) Takeuchi, K.; Akiyama, F.; Miyazaki, T.; Kitagawa, I.; Okamoto, K. *Tetrahedron* 1987, *43*, 701. (b) Takeuchi, K.; Kitagawa, I.; Akiyama, F.; Shibata, T.; Kato, M.; Okamoto, K. *Synthesis* **1987**, 612. (c) Takeuchi, K.; Ikai, K.; Yoshida, M.; Tsugeno, A. *Tetrahedron* **1988**, *44*, 5681.

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Table I. Rates and Rate Ratios for Solvolysis at 25.0 °C[a]

substrate[b]				rate ratio	
system	L[c]	solvent	k, s^{-1}	$\frac{k(X = O)}{k(X = H_2)}$	$\frac{k(X = CH_2)}{k(X = H_2)}$
6a	OTf	EtOH	2.88×10^{-6} [d,e]	$10^{-8.2}$	
6b	OMs	EtOH	2.83×10^{-3} [f,g]		$10^{0.9}$
6c	OMs	EtOH	3.28×10^{-4} [f,h]		
6c	OTf	EtOH	462[i]		
7a	OTf	EtOH	1.04×10^{-4} [j]	$10^{-8.7}$	
7b	n-$C_3F_7CO_2$	80% EtOH	1.04×10^{-7} [d,k]		$10^{-1.1}$
7c	n-$C_3F_7CO_2$	80% EtOH	1.42×10^{-6} [d,l,m]		
7c	Br	EtOH	1.39×10^{-6} [d]		
7c	OTf	EtOH	4.9×10^{4} [n,o]		

[a] Buffered with 0.025 M 2,6-lutidine. For kinetic procedures, see ref 12. [b] For the purities and physical properties, see refs 6, 8, and 9. [c] Leaving group. [d] Determined titrimetrically with an experimental error ±2%. [e] $k = 8.45 \times 10^{-5}$ s^{-1} (50.0 °C); $\Delta H^{\ddagger} = 25.3$ kcal/mol; $\Delta S^{\ddagger} = 0.9$ eu. [f] Determined conductimetrically with an experimental error ±0.5%. [g] $k = 1.53 \times 10^{-2}$ s^{-1} (40.0 °C); $\Delta H^{\ddagger} = 20.3$ kcal/mol; $\Delta S^{\ddagger} = -2.1$ eu. [h] $k = 2.16 \times 10^{-3}$ s^{-1} (40.0 °C); $\Delta H^{\ddagger} = 22.7$ kcal/mol; $\Delta S^{\ddagger} = 1.7$ eu. [i] Estimated by multiplying k of **6c** (L = OMs) by a factor of 1.41×10^{6} in ref 12. [j] See ref 4. [k] Extrapolated from 3.59×10^{-6} s^{-1} (50.0 °C) and 7.46×10^{-5} s^{-1} (75.0 °C); $\Delta H^{\ddagger} = 26.6$ kcal/mol; $\Delta S^{\ddagger} = -1.4$ eu. [l] $k = 3.93 \times 10^{-5}$ s^{-1} (50.0 °C); $\Delta H^{\ddagger} = 24.9$ kcal/mol; $\Delta S^{\ddagger} = -2.0$ eu. [m] Reported value is 2.92×10^{-6} s^{-1}; see ref 10. [n] Estimated by multiplying k of **7c** (L = Br) by a factor of 3.51×10^{10} in ref 12. [o] Previously estimated value was 1.7×10^{4} s^{-1}, see ref 4.

Table II. Bond Orders and Net Atomic Charges for Cations Calculated by AM1[a,b]

	bond order				net atomic charge					
cation precursor	2-oxo cation		2-methylene cation		2-oxo cation			2-methylene cation		
	C(1)—C(2)	C=O	C(1)—C(2)	C=CH_2	C(1)	C(2)	O	C(1)	C(2)	CH_2[c]
3a, 3b	0.890	2.036	1.041	1.917	0.284	0.192	−0.127	0.390	−0.243	−0.078
4a, 4b	0.877	2.030	1.028	1.912	0.288	0.197	−0.125	0.394	−0.245	−0.077
5a, 5b	0.879	2.004	1.087	1.828	0.304	0.196	−0.145	0.379	−0.231	−0.046
6a, 6b	0.881	1.995	1.157	1.737	0.279	0.194	−0.143	0.317	−0.219	0.005

[a] The arrangement of atoms is C(1)—C(2)=O or C(1)—C(2)=CH_2 with C(1) being the bridgehead cationic center. [b] Rate data have not been obtained for **3b** and **4a**. [c] Net atomic charge on carbon.

by treatment with triflic anhydride in methylene chloride in the presence of pyridine.[6] The 2-methylene alcohols for **6b** and **7b** were derived from the corresponding ketols by applying a modified Wittig reaction[7] on the *tert*-butyldimethylsilyl or trimethylsilyl ether, respectively.[8] Since the triflates of **6b**, **6c**, **7b**, and **7c** were expected to be too reactive for measurement of their solvolysis rates, appropriate leaving groups were selected,[9] and the rates of ethanolysis of the triflates for **6c** and **7c** were estimated by using the conversion factors for 1-adamantyl ethanolysis.[12,13] The rate ratio **7b**/**7c** was determined for L = n-$C_3F_7CO_2$ in 80% EtOH. All the substrates followed good first-order kinetics ($r > 0.999$);[17] the rate data are summarized in Table I.

It is noted that the $k(X = CH_2)/k(X = H_2)$ rate ratio at 25 °C increases in the order **4b**/**4c** ($10^{-3.9}$; L = OTf; EtOH),[3] **7b**/**7c** ($10^{-1.1}$; L = n-$C_3F_7CO_2$; 80% EtOH), **5b**/**5c** ($10^{-0.8}$; L = OMs; EtOH),[3] and **6b**/**6c** ($10^{0.9}$; L = OMs; EtOH), indicating increasing π-conjugative ability.[18] It has been reported that when a fully conjugated allylic carbocation intermediate is formed, allylic compounds solvolyze faster than unsubstituted model compounds by a factor of 10^{2}–$10^{2.8}$.[19] Consequently, a reasonable estimate

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(6) **7a** was a stable solid (mp 88.0–89.0 °C) and showed satisfactory microanalytical and spectral data, whereas **6a** was an unstable solid (mp 61–64 °C) and the color changed from white to pale pink on standing at room temperature for a few minutes. The purity of **6a** assessed by ^{13}C NMR was approximately 96%.

(7) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.

(8) 2-Methylenebicyclo[3.3.1]nonan-1-ol (mp 44.5–45.5 °C) and 4-methylenehomoadmantan-3-ol (mp 117.0–118.0 °C) gave satisfactory microanalytical and spectral data.

(9) **6b** was obtained as an oily mixture containing **6b** and the corresponding alcohol **6b**-OH in an approximate molar ratio of 37:63 (by ^{1}H NMR) following a reported method: Bentley, T. W.; Kirmse, W.; Llewellyn, G.; Sollenbohmer, F. *J. Org. Chem.* **1990**, *55*, 1536. That the sole mesylate present was **6b** was evidenced by ^{13}C NMR and by the observation that the ethanolysis product was composed of two components **6b**-OEt and originally included **6b**-OH (39:61 in moles isolated). The ethanolysis rates of crude **6b** before and after aqueous workup agreed with each other within experimental error (±0.5%). **6c** was also obtained as an oil containing approximately 19 mol % (by ^{13}C NMR) of the corresponding alcohol after aqueous workup, which was used for rate studies. The purity of **7b** (oil) was greater than 98% by ^{13}C NMR. **7c** (L = n-$C_3F_7CO_2$)[10] and **7c** (L = Br)[11] were prepared by reported methods.

(10) Fărcaşiu, D.; Jähme, J.; Rüchardt, C. *J. Am. Chem. Soc.* **1985**, *107*, 5717.

(11) Stetter, H.; Goebel, P. *Chem. Ber.* **1963**, *96*, 550.

(12) Takeuchi, K.; Ikai, K.; Shibata, T.; Tsugeno, A. *J. Org. Chem.* **1988**, *53*, 2852.

(13) Generally, the bridgehead reactivity ratio between two skeletal systems is sensibly constant irrespective of the leaving group. Reported data show that the 1-adamantyl/bicyclo[2.2.2]oct-1-yl rate ratio in ethanol at 25 °C is $10^{4.2}$ for triflates[3,12] or $10^{3.9}$ for tosylates.[14,15] In 80% ethanol the latter value merely changes to $10^{4.0}$,[14,15] indicating only slight influence of changing the solvent from ethanol to 80% ethanol. On the other hand, uncertainties of conversion factors for changes in leaving group are estimated to be in the range $10^{\pm 0.2}$ for bridgehead substrates.[16] Consequently, an allowance of $10^{\pm 0.2}$ – $10^{\pm 0.3}$ should be made for $k(X = O)/k(X = H_2)$ ratios. These uncertainties, however, do not alter the conclusion of the present study.

(14) Kevill, D. N.; Kolwyck, K. C.; Weitl, F. L. *J. Am. Chem. Soc.* **1970**, *92*, 7300.

(15) Bentley, T. W.; Bowen, C. T.; Morten, D. H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 5466.

(16) Bentley, T. W.; Roberts, K. *J. Org. Chem.* **1985**, *50*, 5852.

(17) The S_N1 nature in the solvolysis of **6a** and **7a** has been shown by nicely linear mY plots in methanol, ethanol, and aqueous ethanols: the details will be reported in the full paper.

(18) The increasing order of the rate ratios agrees well with the decreasing order of the "olefinic strain", which is defined as the difference between the strain energies (kcal/mol) calculated by molecular mechanics for a bridgehead olefin and a corresponding saturated hydrocarbon, both in the most stable conformations: bicyclo[2.2.2]oct-1-ene, 40.4; homoadamant-3-ene, 20.2; bicyclo[3.2.2]non-1-ene, 19.5; bicyclo[3.3.1]non-1-ene, 15.2: Maier, W. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 1891.

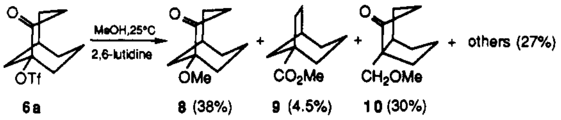
(19) (a) Streitwieser, A., Jr. *Solvolytic Displacement Reactions*; McGraw Hill: New York, 1962; p 79. (b) Tsuji, T.; Moritani, I.; Nishida, S. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2338. (c) Wilcox, C. F., Jr.; Jesaitis, R. G. *Chem. Commun.* **1967**, 1046.

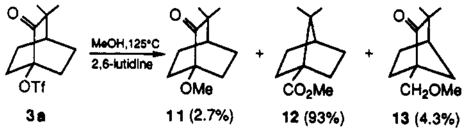
is that as much as 70–80% allylic conjugation is attained in the incipient carbocation from **6b**.

In contrast, the $k(X = O)/k(X = H_2)$ ratios are essentially constant with $10^{-8.7}$ to $10^{-8.2}$. It has been estimated that the full carbonyl π-conjugation in **1** would facilitate the rates of solvolysis of α-keto substrates by a factor of 10^4–10^5.[20] If this were the case, the **6b**/**6c** rate ratio would be 10^{-5} to 10^{-4} as a result of 70–80% carbonyl π-conjugation. A slight increase in the $k(X = O)/k(X = H_2)$ rate ratio in the manner $10^{-8.4}$ (**3a**/**3c**), $10^{-8.3}$ (**5a**/**5c**), and $10^{-8.2}$ (**6a**/**6c**) with the increase in the flexibility of the bicyclic ring system appears to be too small to positively support the π-conjugative effect.

AM1 calculations[21] conducted on the 2-methylene bicyclic bridgehead carbocations showed that with the increase in $k(X = CH_2)/k(X = H_2)$ the C(1)–C(2) bond order increases and the C=C bond order decreases (Table II). In the same sequence the net atomic charge on C(1) decreases and that on the olefinic methylene carbon increases. These results show that our approach is reasonable. Similar calculations on the α-keto bicyclic bridgehead carbocations indicated small decreases in the C=O bond order with increasing structural flexibility. However, the changes appear to be too small to evaluate the significance of the carbonyl π-conjugation. In addition, an inspection of net atomic charge reveals a decreasing trend of charge delocalization on the carbonyl oxygen with increasing ring flexibility, contrary to the expectation if carbonyl π-conjugation were important. More rigorous ab initio calculations on the 2-oxoethyl cation have been reported, and the results also indicate the unimportance of π-conjugation in 1.[1d,22]

The products of solvolysis of **6a** and **7a** were studied in methanolysis in the presence of excess 2,6-lutidine at 25 °C. Although **7a** gave the corresponding bridgehead methyl ether exclusively, **6a** afforded a mixture of bridgehead methyl ether **8** (38%) and rearrangement poducts **9** (4.5%) and **10** (30%), accompanied by several unidentified products amounting to 27%.[23] Very recently, it has been suggested that the preferred formation of rearrangement products **12** (93%) and **13** (4.3%) from **3a**[3] might indicate σ-participation leading to a nonclassical ion in solvolysis.[1d] At the present stage the relative importance of σ-participation is difficult to assess. However, the exclusive bridgehead substitution in the solvolysis of **7a** suggests that the rearrangement is related to the skeletal structure of the first-formed, classical, bridgehead cation rather than the involvement of a nonclassical ion.





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 of **6a**, **6b**, **7a**, **7b**, and their solvolysis products, and 2-oxo and 2-methylene bridgehead alcohols (19 pages). Ordering information is given on any current masthead page.

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[20] Creary, X.; Geiger, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 4151.

[21] *QCPE* 527.

[22] (a) 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. (b) Lien, M. H.; Hopkinson, A. C. *Ibid.* **1988**, *110*, 3788.

[23] The product distribution was determined by GLC (PEG 20M) for the reaction mixture after >10 half-lives and then each product separated by medium pressure column chromatography over silica gel. **9** (oil) was identified on the basis of the retention time in GLC, which agreed with that of an authentic sample. **8** (oil) was identified on the basis of the close resemblance of the ^{13}C NMR spectrum to that of the corresponding ketol. **10** (oil) was transformed to 1-(methoxymethyl)bicyclo[3.3.0]octane by Wolff–Kishner reduction, whose spectral and GLC data agreed with those of an authentic sample. The methanolysis product of **7a** was identified as 3-methoxyhomoadamantan-4-one (mp 56.0–56.5 °C) on the basis of spectroscopic and microanalytical data. **6b** and **7b** were solvolyzed in ethanol and 80% ethanol, respectively, to give only bridgehead substitution products, whose spectral data were consistent with proposed structures.

The First Alkylation of *o*-Carboranes under Essentially Neutral Conditions. Application to the Synthesis of ^{10}B Carriers

Hisao Nemoto, FengGuang Rong, and Yoshinori Yamamoto*

Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan

Received August 13, 1990

Summary: The palladium-catalyzed reaction of 1,2-dicarbora-*closo*-dodecaboranes (*o*-carboranes) (**1**) with allyl ethyl carbonate (**3**) gave 2-allylated *o*-carboranes (**2**) in good to excellent yields. Compounds **2** could be converted to the corresponding diols (**4**), which were soluble in water and thus could be utilized as carriers for ^{10}B neutron capture therapy.

Development of a new synthetic method for ^{10}B carriers[1] with a relatively large number of ^{10}B atoms in the molecule is required in order to deliver a sufficient quantity of ^{10}B atoms to tumor cells. *o*-Carborane (**1**), one of the most stable boron clusters, is an appropriate candidate for use in such a method.[2] One of the most convenient methods for the alkylation of *o*-carboranes is the reaction of electrophiles with carborane carbanions.[3] However, the generation of the carbanion usually requires the use of strong bases, such as butyllithium and alkali metal amides,[4]

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[1] Previous studies for the synthesis of ^{10}B carriers: (a) Yamamoto, Y.; Seko, T.; Nemoto, H. *J. Org. Chem.* **1989**, *54*, 4734. (b) Yamamoto, Y.; Seko, T.; Rong, F.; Nemoto, H. *Tetrahedron Lett.* **1989**, *30*, 7191.

[2] Miura, M.; Gabel, D.; Oenbrick, G.; Fairchild, R. G. *Tetrahedron Lett.* **1990**, *31*, 2247.

[3] Maurer, J. L.; Berchier, F.; Serino, A. J.; Knobler, C. B.; Hawthorne, M. F. *J. Org. Chem.* **1990**, *55*, 838 and the references cited therein.

[4] Niedenzu, K.; Buschbeck, K. C. *Gmelin Handbuch der Anorganischen Chemie*; Bowerbindungen, Springer-Verlag: Berlin, 1978; Vol. 11, p 81.

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