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Solvolysis of 2-Thioxo Bridgehead Compounds as Compared with their 2-Oxo Homologs: Evidence for Marked π-Conjugation in 2-Thioxo Carbocation

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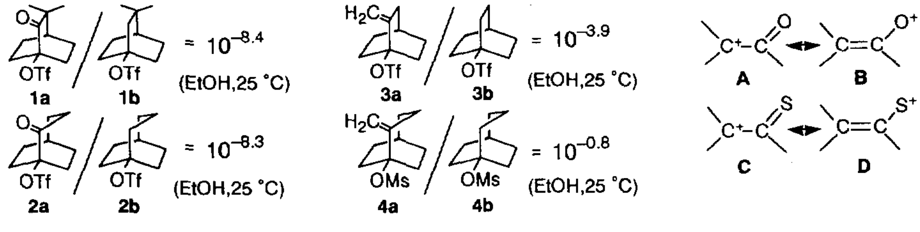
***Abstract*:** The solvolysis rate ratios of 2-thioxo bicyclic bridgehead compounds relative to the parent compounds increase with flexibility of the ring system, supporting the propriety of the authors' methodology for evaluation of the enhancement of π-conjugation with increasing skeletal flexibility. On the basis of the fact that no appreciable stabilization due to carbonyl conjugation has been detected by this approach, the carbonyl π-conjugation in tertiary α-carbonyl cations, if present, is too small to be detected experimentally.

In recent years, various data on the solvolysis rate have been interpreted to support the notion that the α-carbonyl carbocations are stabilized by π-conjugation to an extent which partly offsets the destabilizing inductive effect of the carbonyl group.[1]

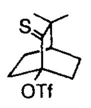
Previously, we have reported that the rates of solvolysis of 3,3-dimethyl-2-oxobicyclo[2.2.2]oct-1-yl triflate (**1a**) and 2-oxobicyclo[3.2.2]non-1-yl triflate (**2a**) relative to their corresponding parent compounds (**1b** and **2b**) are essentially identical ($10^{-8.4}$ for **1a**/**1b** and $10^{-8.3}$ for **2a**/**2b** in EtOH, 25 °C; Scheme 1).[2,3] On the other hand, the rate ratios of 2-methylene substituted derivatives to their corresponding parent compounds increase from $10^{-3.9}$ for **3a**/**3b** to $10^{-0.8}$ for **4a**/**4b**, indicating greater allylic conjugation in the ionization in **4a** than in **3a** (Scheme 1).[2-4] Consequently, the essentially identical rate ratios for **1a**/**1b** and **2a**/**2b** have been interpreted to indicate the unimportance of π-conjugative stabilization of tertiary α-carbonyl cations (**A**↔**B**). Theoretical studies of Lien and Hopkinson also support the unimportance of the resonance contribution of **B**.[5]

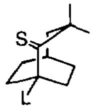
However, the propriety of our methodology has not necessarily been accepted.[1a,c] It has been suggested that **1a** might be a k_Δ substrate because of the preferred formation of a rearrangement product from the methanolysis of **1a**, and that "there is no reason to expect that a constrained α-carbonyl cation will distort in a similar fashion as the C=C bond in a geometrically constrained allylic cation." In order to examine if this methodology serves appropriately as a tool for evaluation of the π-conjugative effect, we extended the work to 2-thioxo cations. In recent years, thiocarbonyl mesomeric stabilization (**C**↔**D**) has been suggested in α-$C(NMe_2)=S$ substituted cations.[6] Theoretical studies also supported this suggestion.[5,7]



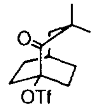
Scheme 1

We now report on the solvolyses of 3,3-dimethyl-2-thioxobicyclo[2.2.2]oct-1-yl triflate (**5a**) and 3,3-dimethyl-2-thioxobicyclo[3.2.2]non-1-yl tresylate (**6a-OTr**) in ethanol buffered with 2,6-lutidine. The π-conjugative effect of the 2-thioxo group (**C↔D**) on the carbocation stability has been evaluated by comparing the rate ratio **5a/1b** with **6a-OTf/2b**. In order to prevent the formation of an enethiol, the C(3)-position of **5a** and that of **6a** have been blocked by two methyl groups. We adopted **2b** as a parent compound of **6a-OTf** instead of 3,3-dimethylbicyclo[3.2.2]non-1-yl triflate because of difficulties in the synthesis. The rate of **2b** is expected to be similar to that of 3,3-dimethylbicyclo[3.2.2]non-1-yl triflate, since the rate of **2a** is roughly the same as that of 3,3-dimethyl-2-oxobicyclo[3.2.2]non-1-yl triflate (**7a**) (Table 1; **7a/2a**=1.5). It is also known that the effect of introducing two methyl groups to the C(3)-position of **3b** on the ethanolysis rate is only 4.2 (k_1=8.99 × 10^{-3} for **1b** and k_1=2.14 × 10^{-3} for **3b** at 25 °C; **1b/3b**=4.2).[2] While the choice of **2b** as the parent compound of **6a-OTf** is not rationalized, its use does not alter the conclusion of the present study.


5a


6a-OTf
6a-OTr

L=leaving group
OTf ; CF_3SO_3
OTr ; $CF_3CH_2SO_3$


7a

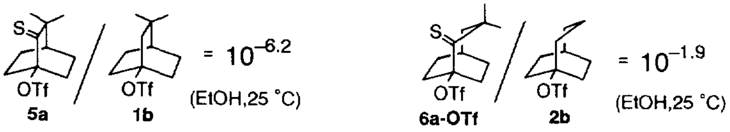
The 2-thioxo alcohols derived from the corresponding ketols via thionation[8] of 2-hydrazono alcohols were converted to the triflate or the tresylate. The rate of **6a-OTf** was expected to be too fast to be measured; therefore, it was estimated from the rate of **6a-OTr** by using the rate ratio k_{OTf}/k_{OTr} = 9.75 × 10^3 determined for the ethanolysis of 1-adamantyl triflate and tresylate at 25.0 °C.[9,10] The rate data are summarized in Table 1.

Table 1. The Rates of Ethanolysis of Various Bridgehead Triflates and Tresylate.[a]

Substrate	k_1 / s^{-1}					ΔH‡	ΔS‡
	0.0 °C	25.0 °C	50.0 °C	75.0 °C	100.0 °C	/kcal mol^{-1}	/cal $K^{-1}mol^{-1}$
5a		6.05 × 10^{-9} [b]	3.14 × 10^{-7}	9.42 × 10^{-6}	1.74 × 10^{-4}	29.7	+3.4
6a-OTf		8.0 × 10^{-1} [c]					
6a-OTr [d]	1.86 × 10^{-6}	8.21 × 10^{-5}				23.9	+3.0
7a		5.73 × 10^{-7} [e]	1.51 × 10^{-5} [e]			24.5	–5.1
2a [f]		3.74 × 10^{-7} [f]	1.10 × 10^{-5} [f]			25.3 [f]	–3.1 [f]

[a] The rates were determined for 0.02M or 0.01M substrates in the presence of 0.025M 2,6-lutidine by titrating the generated acid with 0.01M KOH-EtOH in acetone to bromcresol green-methyl red end point. [b] Extrapolated from data at other temperatures. [c] Estimated by multiplying k_1 of **6a-OTr** by a factor of 9.75 × 10^3 for the OTf/OTr rate ratio of the 1-adamantyl system (ref 10). [d] The unstable **6a-OTr**, obtained as an oil containing the corresponding alcohol and unidentified products, was used without purification after being identified by ^{13}C NMR. The purity of **6a-OTr** was 70–80% (by ^{13}C NMR). [e] Initial rate. [f] See ref 2.

The rate ratios of the 2-thioxo derivatives to their corresponding parent compounds increase from $10^{-6.2}$ for **5a/1b** to $10^{-1.9}$ for **6a-OTf/2b** (Scheme 2). The gain of $10^{4.3}$ (= $10^{-1.9}/10^{-6.2}$), which corresponds to ca. 6 kcal mol^{-1}, is reasonably attributed to the increase in π-conjugation (**C↔D**) in the incipient carbocation from **6a**. The log[k(X = CH_2, S, or O)/k(X = H_2)] values of the bicyclo[2.2.2]oct-1-yl system linearly decrease with the increase of the corresponding field/inductive parameter, σ_F,[11] for -C(C_6H_5)=X calculated from the substituent ^{19}F NMR shielding effect for meta-substituted fluorobenzenes (Fig. 1). Consequently, the


5a / **1b** = $10^{-6.2}$ (EtOH,25 °C)

6a-OTf / **2b** = $10^{-1.9}$ (EtOH,25 °C)

Scheme 2

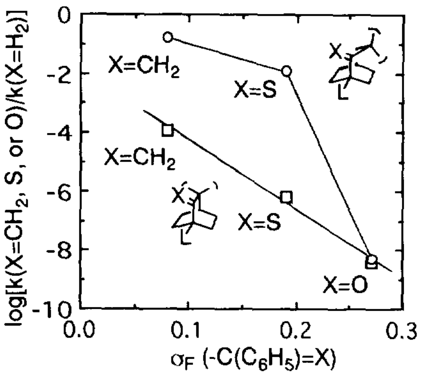


Fig. 1. Plot of log[k(X = CH_2, S, or O)/k(X = H_2)] values against σ_F for -C(C_6H_5)=X calculated from the substituent ^{19}F NMR shielding effect for meta-substituted fluorobenzenes. For σ_F values, see ref 11.

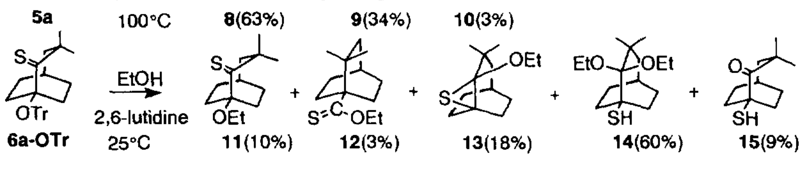
increasing deactivating factors of $10^{3.9}$ for **3a**/**3b**, $10^{6.2}$ for **5a**/**1b**, and $10^{8.4}$ for **1a**/**1b** are ascribed to the increasing electron-withdrawing inductive effects (–I) in the order C=CH_2, C=S, and C=O groups. This linear correlation supports the notion that the cations from the bicyclo[2.2.2]oct-1-yl substrates **3a**, **5a**, and **1a** are free from conjugation because of the perpendicular orientation of the π system and the cationic p orbital.

The almost linear plot implies that the solvolysis mechanisms for the bicyclo[2.2.2]oct-1-yl substrates **1a**, **3a**, and **5a** are similar. In the case of the 2-methylene derivative **3a**, it solvolyzes via a k_C process to give solely a bridgehead substitution product.[2,4] Consequently, it is reasonable to conclude that the solvolyses of **1a**, **3a**, and **5a** proceed via k_C processes. The present result is not consistent with the notion that **1a** may well be a k_Δ substrate and that its rate might be accelerated to some extent by σ-participation.[1a,c]

The development of the thiocarbonyl π-conjugation is represented in Fig. 1 as the upward shift of the point of the log[k(X = S)/k(X = H_2)] value from the bicyclo[2.2.2]oct-1-yl to the bicyclo[3.2.2]non-1-yl system. The point of the log[k(X = CH_2)/k(X = H_2)] value of the bicyclo[3.2.2]non-1-yl system also deviates from the line of the bicyclo[2.2.2]oct-1-yl system. The increasing trend of the log[k(X = S or CH_2)/k(X = H_2)] values supports the postulate that the increase in the ring size from **5a** to **6a** makes the structure more flexible and more susceptible to π-conjugation.

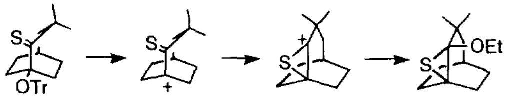
Contrary to the 2-thioxo or 2-methylene analogues, the points of the log[k(X = O)/k(X = H_2)] values remain constant at approximately –8 (Fig. 1). A reasonable interpretation of the marked contrast is that the π-conjugative stabilization of tertiary α-carbonyl cations, if present, is too small to be detected experimentally.

The products of solvolysis of **5a** and **6a-OTr** were studied in ethanolysis in the presence of excess 2,6-lutidine.[12] Although **5a** gave only the normal substitution product **8** and the Wagner-Meerwein rearrangement products **9** and **10**, **6a-OTr** yielded an episulfide **13** and bridgehead thiols **14** and **15** besides smaller amounts



Scheme 3

of the normal substitution product **11** and the Wagner-Meerwein rearrangement product **12** (Scheme 3).[13] The formation of **13** may reasonably be explained in terms of the pathway of Scheme 4. Most probably, the flexible framework of cation **16** enables its cyclization to form episulfide cation **17** that leads to **13** and then to **14**.[14]



6a-OTr **16** **17** **13**

Scheme 4

In summary, the marked π-conjugative effect of the 2-thioxo group on the carbocation stability has been demonstrated by comparing the rate ratio of the **5a/1b** with **6a/2b**. The increase in the rate ratios with flexibility of the ring system supports the applicability of our methodology to detect the enhancement of π-conjugation with increasing skeletal flexibility. On the basis of the fact that no appreciable stabilization due to carbonyl conjugation has been detected by our approach, the carbonyl π-conjugation in tertiary α-carbonyl carbocations, if present, is believed to be too small to be detected by solvolysis studies.

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9. Although **6a-OTf** was identified by ^{13}C NMR in the reaction mixture containing the corresponding alcohol and unidentified products, it rapidly decomposed in aqueous workup at 0 °C. **6a-OTr**; ^{13}C NMR ($CDCl_3$, 100.4 MHz), δ 24.9 (CH_2), 28.2 (CH), 33.7 (CH_2), 35.7 (CH_3), 48.3 (CH_2), 53.0 (C), 55.9 (CH_2CF_3; q, J = 32.9 Hz), 103.9 (C), 121.1 (CF_3; q, J = 277.2 Hz), 262.3 (C).
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12. The solvolyses were conducted for 10–20 half-lives. The products were isolated by medium-pressure liquid chromatography and identified spectrophotometrically. The distribution of the products from **6a-OTr** was determined by ^{13}C NMR for the crude product.
13. **11**: red liquid; ^{13}C NMR ($CDCl_3$, 67.8 MHz), δ 15.7 (CH_2), 25.0 (CH_2), 29.1 (CH), 32.4 (CH_2), 35.8 (CH_3), 48.4 (CH_2), 52.4 (C), 57.9 (CH_2), 90.5 (C), 270.7 (C). **13**: liquid; ^{13}C NMR ($CDCl_3$, 100.4 MHz), δ 15.2 (CH_3), 25.7 (CH_2), 27.7 (CH_3), 30.9 (CH_3), 31.7 (CH_2), 31.8 (CH_2), 32.0 (CH), 36.7 (CH_2), 41.1 (C), 50.9 (CH_2), 51.5 (C), 67.6 (CH_2), 91.1 (C). **14**: liquid; ^{13}C NMR ($CDCl_3$, 100.4 MHz), δ 15.3 (CH_3), 27.7 (CH_2), 28.1 (CH), 29.7 (CH_3), 35.0 (CH_2), 43.0 (C), 48.5 (CH_2), 57.5 (C), 59.9 (CH_2), 106.0 (C).
14. We assume that the direct formation of **17** through "frontside S_N2" of **6a-OTr** would be highly improbable. The α-carbonyl thiol **15** is assumed to have been formed during work-up.

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