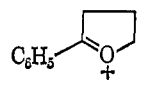
The Synthesis and Acetolysis of the Epimeric 7-Tosyloxynorbornan-2-ones[1]

Paul G. Gassman,[2] James L. Marshall,[3a] and Joseph M. Hornback[3b]

Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received April 15, 1969*

Abstract: *anti*-7-Hydroxynorbornan-2-one *p*-toluenesulfonate (**3**) and *syn*-7-hydroxynorbornan-2-one *p*-toluenesulfonate (**4**) have each been prepared *via* two alternate synthetic routes. Solvolysis of these epimeric tosylates showed that **3** underwent acetolysis more than 10^4 times faster than **4** (at 200°). Comparison of the rate of acetolysis of **3** to that of 7-tosyloxynorbornane showed a relative rate difference of 2×10^7 at 25°. The acetolysis of **3** gave *anti*-7-acetoxynorbornan-2-one as the only product, while both *syn*-7-acetoxynorbornan-2-one and *anti*-7-acetoxynorbornan-2-one were obtained in the acetolysis of **4**. These observations are consistent with the acetolysis of **3** occurring *via* the formation of the enol of **3** followed by solvolysis of this enol with neighboring group participation of the π electrons of the enol double bond. This theory was demonstrated to be correct through the solvolysis of **3** in acetic acid-O-*d* where deuterium incorporation during the enol–keto tautomerism placed a deuterium α to the carbonyl. Since enol formation was part of the over-all rate-determining scheme, an increasing deuterium isotope effect was noted as the reaction proceeded (as the amount of α-deuterium increased). This rate decrease due to the incorporation of deuterium required that the enol be involved as the solvolyzing intermediate. These observations established a new route for neighboring group participation of the carbonyl function.

The recent literature contains numerous examples of neighboring group participation by ketonic carbonyl functions,[4,5] enol ethers,[6] and enolate anions.[7] In the case of 4-halobutyrophenone and 5-halovalerophenone, the intermediates **1** and **2**, respectively, were observed by nmr and isolated as their hexachloroantimonate salts.[4] In addition it has been shown that the presence of a carbonyl group in the γ or δ positions results in an increased rate of solvolysis of an appropriately situated leaving group.[4,5] Although this role of



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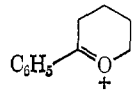

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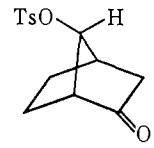
the ketonic carbonyl group is well established, relatively little is known about the influence of the small amount of enol which exists in equilibrium with the keto form. This paper presents the details of our studies on carbonyl neighboring group participation *via* enolization.

As part of our general program of study of the chemistry of 7-substituted norbornanes we investigated the rates of acetolysis of *anti*-7-hydroxynorbornan-2-one *p*-toluenesulfonate (**3**) and *syn*-7-hydroxynorbornan-2-one *p*-toluenesulfonate (**4**). At 200° a difference of 10^4 was observed in the relative rates of acetolysis of **3** and **4**. In addition, a divergence of 2×10^7 existed between the rates of acetolysis of **3** and 7-hydroxynorbornane *p*-toluenesulfonate (**5**) at 25°. Clearly, **3** was undergoing solvolysis much more rapidly than would be expected considering the electron-withdrawing nature of the carbonyl group in the 2 position of **3**. In addi-



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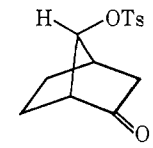

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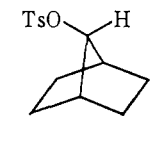

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tion the difference of 10^4 between the rates of acetolysis of **3** and **4** was much larger than what would be expected on the basis of the difference in orientation of the carbonyl dipoles in the epimeric keto tosylates. In view of the anomalously rapid rate of ionization of **3** we have carried out a detailed investigation of the effect of neighboring ketone functions on the solvolysis of tosylate groups in the 7 position of the norbornane skeleton.[8]

Synthesis and Solvolysis

The synthesis of **3** was accomplished by two alternate routes both of which started with *exo*-2-*anti*-7-dihydroxynorbornane[9] (**6**). Oxidation of **6** with chromic acid in water gave the known keto alcohol **7**.[10] Conversion of **7** into **3** was accomplished according to standard procedures.[11,12] The preparation of **3** was also accomplished by the conversion of **6** into the ditosylate **8**. Solvolysis of **8** in 60:40 dioxane–water at 100° gave a 75:25 mixture of **9** and **10**, respectively. Oxidation

(1) For a preliminary account of part of this work, see P. G. Gassman and J. L. Marshall, *J. Am. Chem. Soc.*, **88**, 2599 (1966). See also P. G. Gassman, J. M. Hornback, and J. L. Marshall, *ibid.*, **90**, 6238 (1968); J. T. Lumb and G. H. Whitham, *Chem. Commun.*, 400 (1966).

(2) Alfred P. Sloan Foundation Research Fellow, 1967–1969.

(3) (a) National Science Foundation Cooperative Predoctoral Fellow, 1962–1963, 1964–1966; (b) National Science Foundation Trainee, 1965–1968.

(4) For a leading reference, see H. R. Ward and P. D. Sherman, Jr., *J. Am. Chem. Soc.*, **90**, 3812 (1968).

(5) D. J. Pasto, K. Garves, and M. P. Serve, *J. Org. Chem.*, **32**, 774 (1967); D. J. Pasto and M. P. Serve, *J. Am. Chem. Soc.*, **87**, 1515 (1965).

(6) F. C. Uhle, *J. Org. Chem.*, **31**, 4193 (1966); F. C. Uhle, *ibid.*, **32**, 792 (1967).

(7) A. R. Davies and G. H. R. Summers, *J. Chem. Soc., C*, 909 (1967); F. Nerdel, D. Frank, and K. Rehse, *Ber.*, **100**, 2978 (1967); F. Nerdel, D. Frank, K. Gerner, and W. Metasch, *Tetrahedron Letters*, 4499 (1967).

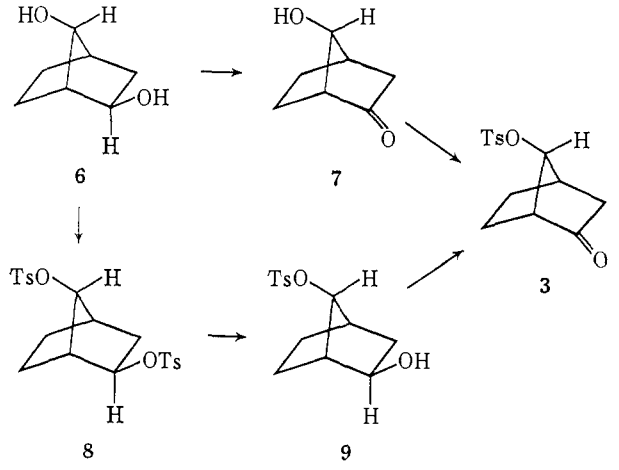
(8) This present paper deals with enolizable ketone functions. For details of the effect of neighboring carbonyl groups in nonenolizable positions, see P. G. Gassman and J. M. Hornback, *J. Am. Chem. Soc.*, **91**, 0000 (1969).

(9) J. K. Crandall, *J. Org. Chem.*, **29**, 2830 (1964).

(10) H. Krieger, *Ann. Acad. Sci. Fennicae, Ser. A, II*, 109 (1962). See also W. E. Meyer, Ph.D. Thesis, New York University, 1964.

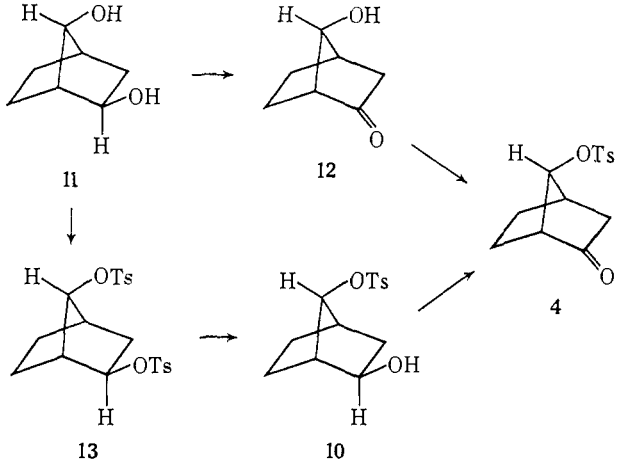
(11) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

(12) Subsequent to the completion of this work we learned that **3** had also been prepared by G. H. Whitham and S. C. Lewis. For details see S. C. Lewis, Ph.D. Thesis, University of Birmingham, England, 1964.



of this mixture with chromic acid in acetic acid[13] gave the corresponding mixture of **3** and **4**. Chromatography on silica gel permitted the isolation of **3** which was shown to be identical with the material prepared from **7** through ir and nmr spectral analyses and mixture melting point measurement.[14]

The synthetic routes to **4** were similar to those used in the preparation of **3**. Oxidation of **11**[15] with chromic acid in water gave *syn*-7-hydroxynorbornan-2-one (**12**)[16] which was readily converted to **4**. Owing to the extreme lability of **12**, this material, which contained a



small amount of unoxidized **11**, was not purified prior to esterification with *p*-toluenesulfonyl chloride. Thus **4** was contaminated with a small amount of **13**. The keto tosylate **4** was separated from **13** by utilization of Girard "T" reagent[17] to give **4**, mp 63.8–64.6°.

The synthesis of **4** was also accomplished through the conversion of **11** into the ditosylate **13** followed by solvolysis of **13** in refluxing 60:40 dioxane–water to give **10** (probably contaminated with **9**). Oxidation of the crude solvolysis product with chromic acid in acetic acid gave **4** which after Girard separation[18] and recrystallization melted at 95.6–96.1°. This material had a melting point and ir spectrum (KBr pellet) different from the sample of **4** obtained from **12**. That the two routes produced the same compound in allotropic forms was established by nmr and solution ir spectral analyses. Subsequent preparations of **4** by either route gave only the higher melting allotrope.

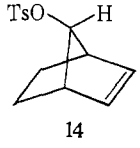
The solvolyses of **3** and **4** were carried out in glacial acetic acid buffered with sodium acetate. The rate data are listed in Table I together with the rates of acetolysis

Table I. Acetolysis Rates of Various 7-Norbornyl Tosylates

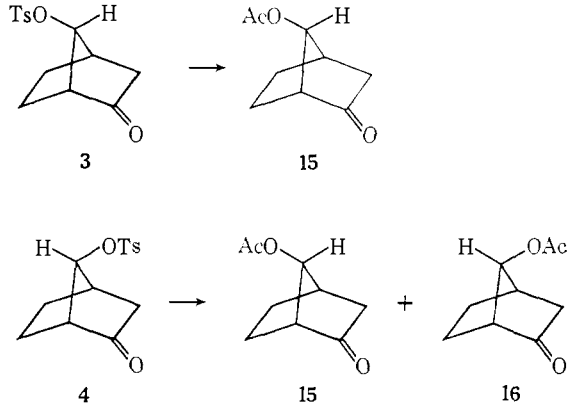
Compd no.	Ref	Temp, °C	Rate, sec^{-1}	H^*, kcal/mole	S^*, eu
4		200.0	$(5.45 \pm 0.19) \times 10^{-6}$	34.9	−9.8
		210.0	$(1.20 \pm 0.00) \times 10^{-5}$		
3		90.0	$(1.13 \pm 0.06) \times 10^{-5}$	22.0	−20.7
		100.0	$(2.78 \pm 0.09) \times 10^{-5}$		
		110.0	$(6.88 \pm 0.01) \times 10^{-5}$		
		(200)[a]	2.08×10^{-2}		
		(25)[a]	1.28×10^{-8}		
5	19	(200)[a]	5.49×10^{-5}	35.7	−3.5
		(25)[a]	6.36×10^{-15}		
14	19	(25)[a]	9.04×10^{-4}	23.3	5.7

[a] Extrapolated rate constants.

of 7-tosyloxynorbornane[19] (**5**) and *anti*-7-tosyloxynorbornene (**14**)[19] for comparison. The acetolysis of **3** gave only *anti*-7-acetoxynorbornan-2-one (**15**) in 63%



yield.[20] Whereas the acetolysis of **3** was unusually clean the acetolysis of **4** was rather complex. When the solvolysis was carried to completion extensive decomposition occurred due to the poor stability of the reac-



(13) For an example of the oxidation of a hydroxy tosylate to the corresponding keto tosylate, see N. A. Nelson and G. A. Mortimer, *J. Org. Chem.*, 22, 1146 (1957).

(14) The formation of the mixture of **9** and **10** from pure **8** was obviously the result of a 6,2-hydride shift. Ample precedent exists for such shifts: J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, 76, 4501 (1954); J. D. Roberts and C. C. Lee, *ibid.*, 73, 5009 (1951).

(15) H. Kwart and W. G. Vosburgh, *ibid.*, 76, 5400 (1954).

(16) This compound has also been prepared by K. Mislow and W. E. Meyer. For details, see W. E. Meyer, Ph.D. Thesis, New York University, 1964.

(17) For a typical procedure, see L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, 1957, pp 88–89.

(18) Pure **4**, uncontaminated by **3**, could be obtained from the crude sample of **10** because any **3**, which would have been formed if **9** were present, would have been destroyed under the conditions of the Girard separation.

(19) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Am. Chem. Soc.*, 77, 4183 (1955).

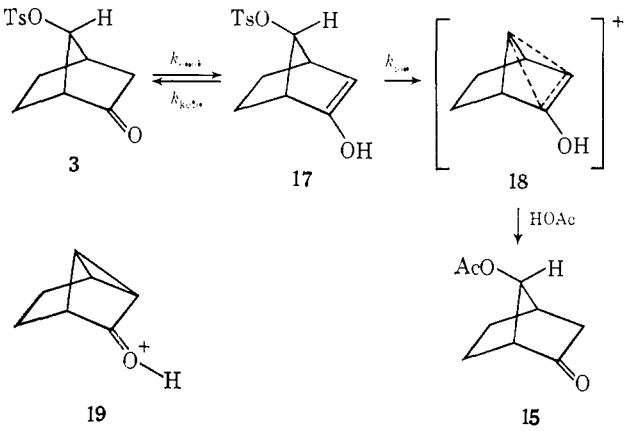
(20) No other products were observed by vpc analysis. However, due to the almost identical retention times of **15** and **16** on a variety of column materials, the lower limit of detection of **16** would have been *ca.* 3%.

tion products in acetic acid at 200°. On very short reaction times (*ca.* 5% reaction) vpc analysis showed that **4** gave one major product, **15**, one minor product, **16**, and three trace components. The ratio of **15** to **16** was 95:5 and it was shown that under the reaction conditions **15** and **16** were not interconverted.

Discussion and Results

From Table I we see that placing an electron-withdrawing carbonyl function in the 2 position of **5** *anti* to the tosylate group increased the rate of acetolysis by *ca.* two million (at 25°). In addition this rate enhancement occurred when the electronic nature of the carbonyl group should have caused a rate decrease. Indeed placing the carbonyl *syn* to the leaving tosylate group, as in **4**, did provide the anticipated decrease in rate. Product studies also indicated that the acetolysis of **3** was not a simple reaction. Whereas **4** gave a mixture of **15** and **16** with inversion of configuration at C-7 predominating, **3** gave complete retention of configuration. Clearly the acetolysis of **3** was far more complex than simple solvolytic ionization of the carbon–tosylate bond. This complexity was also implied by the differences in the thermodynamic parameters listed in Table I.

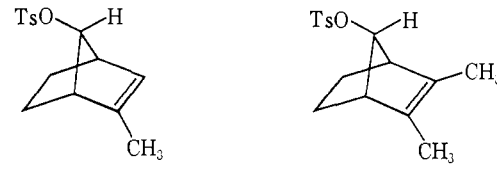
The combination of rate data and product analyses suggested that the ionization of **3** might not involve the keto form of **3**. Rather it seemed probable that the actual solvolyzing intermediate might be the enol form of **3**. The enol, **17**, which has a close structural relationship to *anti*-7-tosyloxynorbornene (**14**), would be expected to undergo solvolysis with participation of the olefinic π electrons.[19,21] Different theories of the nature of this type of neighboring group participation



3 17 18 19 15

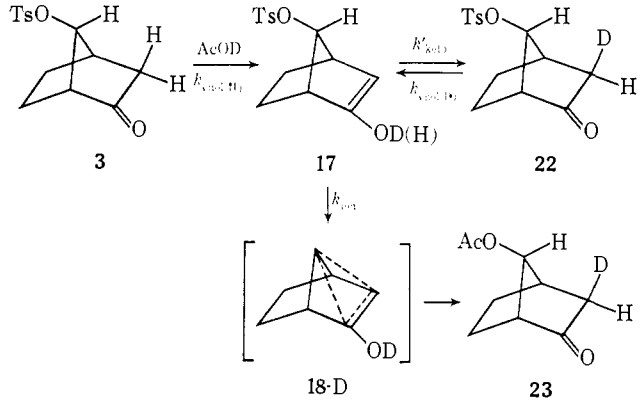
would suggest that **17** could ionize to either the nonclassical ion,[22] **18**, or to the classical ion,[23] **19**. Either of these ions would be expected to collapse to the observed product, **15**. However, the recent studies of the solvolysis of **20** and **21**, in which the rate acceleration due to the methyl substitution was cumulative, provided strong evidence that π electron participation, even in unsymmetrically substituted *anti*-7-tosyloxynorbornenes, was occurring *via* a symmetrical (nonclassical) transition state. Thus we feel that **17** probably undergoes ionization *via* a transition state which resembles **18** more than **19**.[24]

(21) W. G. Woods, R. A. Carboni, and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 5653 (1956).
(22) S. Winstein, A. H. Lewin, and K. C. Pande, *ibid.*, **85**, 2324 (1963).
(23) H. C. Brown and H. M. Bell, *ibid.*, **85**, 2324 (1963).



20 21

Our proposed mechanism requires that enolization be the rate-controlling step with both k_{keto} and k_{ion} representing relatively fast steps in comparison to k_{enol}. Under acid-catalyzed conditions, such as were present in our acetolysis,[25] the rate-determining step in the enolization process is removal of the α-proton subsequent to rapid proton addition to the carbonyl.[26,27] If our proposed mechanism was correct, replacement of the α-proton by an α-deuterium should show a rate change as a result of a primary deuterium isotope effect. The labeled ketone, **22**, would be the ideal molecule for such a study. Unfortunately, the possible synthetic routes to **22** were fraught with complications. However if the rate of return of the enol to the keto form, k_{keto}, and the rate of ionization of the enol, k_{ion}, were of the same order of magnitude, the actual synthesis of pure **22** would not be required because solvolysis in acetic acid-O-*d* would result in partial deuterium incorporation. As the amount of deuterium in the α position increased, the rate of the reaction should undergo a corresponding decrease. Fortunately, k_{ion} and k'_{keto} were of the same order of magnitude. Enolization of **3** gave **17** which in acetic acid-O-*d* ketonized to **22** and ionized fo **18-D**



3 17 22 18-D 23

(which collapsed with solvent to give **23**). The solution now contained both **3** and **22**. Since $k_{enol(D)}$ was slower than $k_{enol(H)}$, a decreasing rate was observed as shown in Figure 1. As illustrated, **3** in acetic acid-O-*d* gave a constantly changing rate curve whereas **3** in normal acetic acid gave excellent pseudo-first-order kinetics. Table II lists the rate constants for three 7-tosyloxynorbornanes in both protio- and deuterioacetic acid. As shown in Table II, the rate of solvolysis of **3** changed by a factor of *ca.* 7 during the first 80% of the reaction. This sevenfold decrease of rate in going from **3** as the major reactant to a mixture which had predominately **22**

(24) P. G. Gassman and D. S. Patton, *ibid.*, **91**, 2160 (1969). However, it should be noted that whereas the alkyl groups stabilize incipient positive charge inductively, the oxygen function can stabilize through resonance. Thus an intermediate such as **19** must be given serious consideration.
(25) The small amount of sodium acetate present in the acetolysis solvent would have a negligible effect on the rate of enolization of **3**.[26]
(26) C. G. Swain, A. J. DiMilo, and J. P. Cordner, *J. Am. Chem. Soc.*, **80**, 5983 (1958).
(27) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, pp 140–154.

Table II. Acetolysis Rates of Various 7-Tosyloxynorbornanes in Deuterated and Nondeuterated Acetic Acid

Compd	Temp, °C	AcOH rate, rate, sec^{-1}	AcOD	
			Initial rate, sec^{-1}	Final rate, sec^{-1} [a]
3	110.00	$(6.88 \pm 0.01) \times 10^{-5}$	$(1.31 \pm 0.02) \times 10^{-4}$	$(1.94 \pm 0.09) \times 10^{-6}$ [b]
5	200.0	5.49×10^{-5}	$(5.73 \pm 0.01) \times 10^{-5}$	$(5.73 \pm 0.01) \times 10^{-5}$ [c]
4	200.0	5.45×10^{-6}	5.76×10^{-6}	*d*

[a] The final rates listed are the final measured rates and in the case of **3** represent a maximum final rate. At time equal to ten half-lives the rate should be less than the final rate listed for **3**. [b] This rate constant corresponds to the value obtained from the last three points on the dotted curve in Figure 1. [c] Excellent pseudo-first-order kinetics were observed for **5** over 75% reaction. [d] Owing to the extensive decomposition which occurred in the acetolysis of **4**, the rate in acetic acid-O-*d* was only followed to 15% reaction. Good pseudo-first-order kinetics were observed.

as the major reactant was in excellent agreement with the primary deuterium isotope effect of eight observed for the acid-catalyzed enolization of perdeuterioacetone.[28] In comparison **5** showed excellent pseudo-first-order kinetics over two half-lives in acetic acid-O-*d*.

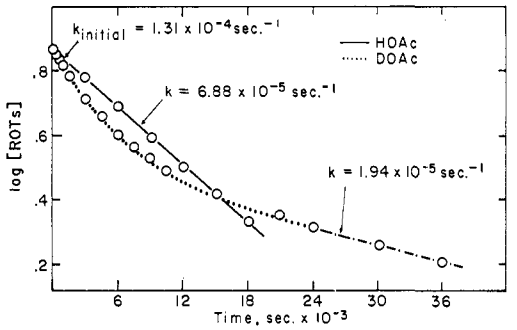
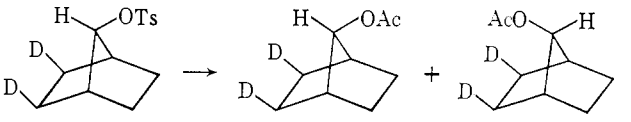


Figure 1. Acetolysis rate curves of *anti*-7-hydroxybicyclo[2.2.1]-heptan-2-one *p*-toluenesulfonate in acetic acid and in acetic acid-O-*d* at 110°.

Related to the kinetic evidence for deuterium incorporation *via* enolization was the isolation of a mixture of **3** and **22** after partial reaction. Mass spectral analysis[29] for the presence of deuterium in a sample of tosylate recovered after 39% solvolysis in acetic acid-O-*d* showed 34% deuterium incorporation corresponding to *ca.* 2:1 ratio of **3**:**22** at this stage of the solvolysis.

Certain other points merit discussion in relation to the over-all study of the mechanism of acetolysis of **3**. In particular the solvent isotope effect was of interest. The ratios of the acetolysis rates in acetic acid-O-*d* to those in protioacetic acid were 1.04 for **5** and 1.06 for **4**. These differ considerably from the ratio of 1.90 observed for the initial rates of solvolysis of **3** in acetic acid *vs.* acetic acid-O-*d*. In general solvent deuterium isotope effects for the solvolysis of aryl sulfonates in deuterium oxide *vs.* water are about 1.10. This value is for simple cases in which carbonium ion formation was the rate-determining step.[30] Our results with **4** and **5** indicate that the solvent deuterium isotope effect in acetic acid is similar to those noted for water. The solvent deuterium isotope effect of 1.90 observed for the acetolysis of **3** provided additional evidence that the rate-determining step was not ionization of the C–OTs bond to form a carbonium ion. Indeed the solvent deuterium isotope effect of 1.90 for **3** was consistent with those found for other enolization studies carried out in deuterated and nondeuterated solvents under acid-catalyzed conditions.[28,31]

The last point of discussion centers on the predominant inversion of configuration at C-7 which occurred in the solvolysis of **4**. In view of the overwhelming retention of stereochemistry observed in the acetolysis of 7-acetoxy-2,3-dideuterionorbornane (**24**), the inversion at C-7 in the acetolysis of **4** was rather surprising. Acetolysis of **24** gave 90% of a 90:10 mixture of **25** and **26**, respectively,[32] or 90% retention. This is contrasted with the 95% inversion of configuration at C-7 in the acetolysis of **4**. We feel that the inversion observed in this solvolysis was the result of the direct displacement of tosylate to the extent of *ca.* 90%. As noted above, **4** solvolyzes about ten times slower than **5**, indicating the inductive retardation of the rate due to the electron-withdrawing nature of the carbonyl. Apparently, in addition to slowing the over-all rate of reaction, the carbonyl group causes a dramatic increase in the SN2 character of the ionization process involved in the acetolysis of the tosylate function of **4**.



24 **25** **26**

In conclusion, we have shown that the rate-determining step in the acetolysis of **3** was enolization of the carbonyl group. This was consistent with the results of rate studies, product studies, primary deuterium isotope effects, and solvent deuterium isotope effects. These results established the significant role which the small amount of enol can play in "carbonyl" neighboring group participation. It is anticipated that "carbonyl" participation *via* the enol form should be a general phenomenon in systems where the rigid geometry of the substrate molecule precludes direct interaction of the electrons associated with the carbonyl oxygen with the incipient carbonium ion center.

Experimental Section[33]

exo-**2**-*anti*-**7-Bicyclo[2.2.1]heptanediol (6).** The method of Crandall[9] was used in the preparation of **6**.

anti-**7-Hydroxybicyclo[2.2.1]heptan-2-one (7).** To a solution of 4.965 g of **6** in 21 ml of water kept at 20–30° was added with stirring 18.5 ml of 6 *M* chromic acid over a period of 40 min. The mixture was cooled to 0° and stirred for 30 min. Isopropyl alcohol (1 ml)

(28) O. Reitz, *Z. Elektrochem.*, 43, 659 (1937).
(29) We wish to thank Dr. Rodger Foltz of Battelle Memorial Institute for the mass spectral analysis.
(30) E. R. Thorton, "Solvolysis Mechanisms," The Ronald Press Co., New York, N. Y., 1965, pp 212–214.
(31) S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, 87, 3228 (1965).
(32) (a) P. G. Gassman and J. M. Hornback, *ibid.*, 89, 2487 (1967); (b) F. B. Miles, *ibid.*, 89, 2488 (1967); 90, 1265 (1968).
(33) Melting points and boiling points are uncorrected.

was added and the reaction mixture was stirred for an additional 10 min. The mixture was extracted with four 30-ml portions of ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield a clear oil. Pressures down to 1 mm were necessary to ensure that no residual ethyl acetate would be present in the following chromatography. The oil was chromatographed through 150 g of silica gel. Elution with methylene chloride–ether gave 1.0 g (20%) of a white solid. Since this material was prone to decompose readily under mild conditions it was used in the next step without further purification.

anti-**7-Hydroxybicyclo[2.2.1]heptan-2-one *p*-Toluenesulfonate (3).** The purity of **7** used in this preparation was found to be very important. All fractions obtained in the chromatography immediately above which were not at least semisolid were discarded, regardless of the appearance of their infrared spectra. Inclusion of these inferior fractions in this preparation rendered the **3** obtained by this route difficult, it not impossible, to purify to a satisfactory degree, and lowered yields drastically.

To a solution of 1.0 g of **7** in 15 ml of pyridine cooled to 0° was added 1.75 g of *p*-toluenesulfonyl chloride. The resulting solution was stored at 5° for 40 hr and then mixed with 150 ml of water and extracted with three 50-ml portions of methylene chloride. The combined extracts were washed with 30 ml of 20% sulfuric acid and 10 ml of water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to a crystalline solid. Recrystallization from hexane gave 1.46 g (84%) of white flakes, mp 95.0–96.5°. Further recrystallization from hexane gave an analytical sample of **3**, mp 95.0–96.5°.

Anal. Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75; S, 11.44. Found: C, 60.06; H, 5.80; S, 11.33.

exo-**2-***anti*-**7-Bicyclo[2.2.1]heptanediol Di-*p*-toluenesulfonate (8).** A 0.80-g sample of **6** was converted to the ditosylate as described below for **11** to yield 1.60 g (59%) of **8**. Recrystallization from methanol gave an analytical sample, mp 129.5–131.5°.

Anal. Calcd for $C_{21}H_{24}O_6S_2$: C, 57.78; H, 5.54; S, 14.69. Found: C, 57.78; H, 5.61; S, 14.68.

anti-**7-Hydroxybicyclo[2.2.1]heptan-2-one *p*-Toluenesulfonate (3) *via* Solvolysis of *exo*-2-*anti*-7-Bicyclo[2.2.1]heptanediol Di-*p*-toluenesulfonate in Dioxane–Water.** A 10.6-g sample of **8** was solvolyzed in dioxane–water and subsequently oxidized with chromic acid–acetic acid as described in detail for the epimer (**13**) (see below) to give 5.1 g of crude crystalline product. This product was recrystallized from hexane to give white crystals, mp 83–90°. This material proved to consist of a 75:25 ratio of **3** to **4** by the following procedure. A sample was acetolyzed to give a rate constant identical with that of an authentic sample of **3**. The infinity titer, however, indicated that the sample consisted of only 75% of **3**. The impurity was isolated by heating a solution of 596 mg of the 83–90° sample in 20 ml of acetic acid (buffered with 0.1 *M* sodium acetate) at 150° for 100 min (to acetolyze completely all **4** present), mixing the resulting solvolysis mixture with 400 ml of water, neutralizing the mixture by the slow addition of 30 g of sodium bicarbonate with stirring, and extracting the mixture with two 100-ml portions of ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and chromatographed through 15 g of silica gel eluting with benzene–ether to give two fractions. In addition to the acetate (**15**) (130 mg, 48% of theoretical) arising from the solvolysis of **3**, a 136-mg sample of **4** was obtained (92% of theoretical).

It was very difficult to obtain a pure sample of **3** from the 83–90° material. Successive attempts at chromatography through silica gel using a benzene–ether eluent afforded white crystals: mp 92.0–95.5°; mixture melting point with an authentic sample of **3**, mp 92.5–95.7°. The nmr pattern and solution infrared spectrum (carbon disulfide) of this material were identical with those of an authentic sample of **3**. The 92.0–95.5° material was obtained in 49% over-all yield from **8**.

exo-**2-***syn*-**7-Bicyclo[2.2.1]heptanediol (11).** The preparation of **11** was carried out according to the method of Kwart and Vosburgh.[15]

syn-**7-Hydroxybicyclo[2.2.1]heptan-2-one (12).** To a stirring solution of 12.64 g of **11** in 300 ml of reagent grade acetone cooled to 0° was added 37 ml of 6 *M* chromic acid over a period of 1.5 hr with precautions taken to exclude external moisture.[34] After stirring for a subsequent 0.5 hr the supernatant liquid was decanted, and the residue was washed thoroughly with acetone. The combined acetone phases were dried with anhydrous magnesium sulfate and concentrated under reduced pressure without external heating. The resulting residue was dissolved in 500 ml of ether, washed with three 15-ml portions of saturated sodium bicarbonate solution and with 15 ml of water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to a yellow oil which crystallized in cyclohexane. Recrystallization from cyclohexane gave 2.59 g of white crystals, mp 140–155°. Vapor phase chromatography indicated that the product was a mixture of **11** and **12** in the respective ratio of *ca.* 40:60.

Attempts to increase the per cent composition of **12** in the product, by increasing the relative amount of chromic acid used, was unsuccessful. With excess oxidizing agent extensive decomposition was noted. Owing to the extremely unstable nature of **12**, it was used in the next step without further purification.

syn-**7-Hydroxybicyclo[2.2.1]heptan-2-one *p*-Toluenesulfonate (4) *via* Jones Oxidation of 11.** A sample of **11** was oxidized by the above procedure to yield 6.1 g of crude **12**. The crude product was dissolved in 40 ml of pyridine and cooled to 0°. With stirring was added 14.1 g of *p*-toluenesulfonyl chloride. The resulting solution was allowed to stand at 5° for 41 hr. The resulting pink solution was mixed with 500 ml of water and extracted with four 50-ml portions of chloroform. The combined extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to a purple oil. The oil was decolorized with charcoal in ether to yield 7.3 g of a yellow oil, which was dissolved in 75 ml of 95% ethanol. To this solution were added 4.28 g of Girard's "T" reagent (Arapahoe Chemicals, Inc.) and 1 ml of glacial acetic acid. The resulting solution was refluxed for 4.5 hr, cooled, and mixed thoroughly with a mixture of 400 ml of water and 400 ml of ether. The aqueous layer was drawn off and to it was added 1 ml of concentrated hydrochloric acid. The aqueous phase was heated on a steam bath for 3.5 hr, cooled, and extracted with two 200-ml portions of ether. The combined extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to a yellow oil. Hot hexane washings gave, when cooled, 1.30 g (17% based on crude **12** of 60% purity) of white crystals. Recrystallization from hexane gave an analytical sample of **4**, mp 63.8–64.6°.

Anal. Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75; S, 11.44. Found: C, 59.93; H, 6.05; S, 11.61.

Subsequent preparations of **4** by this procedure resulted in formation of the allotrope, mp 95.0–95.5°.

Preparation of 4 *via* Chromic Acid in Water Oxidation of 11. To a stirring solution of 55 g of **11** in 250 ml of water cooled to 0° was added 210 ml of 6 *M* chromic acid over a period of 0.5 hr. After 15 min of additional stirring, 10 ml of isopropyl alcohol was added. After stirring for an additional 15 min, the mixture was extracted with four 100-ml portions of ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to a brown oil. Formation of the tosylate and subsequent Girard separation as above gave after recrystallization from hexane 1.78 g (1.5% over-all) of **4** as fine white needles, mp 93.0–94.0°.

exo-**2-***syn*-**7-Bicyclo[2.2.1]heptanediol Di-*p*-toluenesulfonate (13).** To a solution of 4.02 g of **11** in 25 ml of pyridine cooled to 0° was added with stirring 12.9 g of *p*-toluenesulfonyl chloride. The resulting solution was stored at 5° for 20 hr and then poured over 750 ml of water and extracted with three 125-ml portions of chloroform. The combined extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to a clear syrup. Crystallization from methanol in a Dry Ice–isopropyl alcohol bath gave 10.54 g (77%) of white powdery crystals, mp 111–115°. Recrystallization from methanol–ether gave an analytical sample of **13**, mp 121.5–121.6°.

Anal. Calcd for $C_{21}H_{24}O_6S_2$: C, 57.78; H, 5.54; S, 14.69. Found: C, 57.70; H, 5.63; S, 14.53.

syn-**7-Hydroxybicyclo[2.2.1]heptan-2-one *p*-Toluenesulfonate (4) *via* Solvolysis of 13 in Dioxane–Water.** A solution of 5.82 g of **13** in 100 ml of 60:40 dioxane–water (v/v) was refluxed for 37 hr and then cooled. An excess of sodium bicarbonate was added. After effervescence had subsided, the mixture was concentrated under reduced pressure to a semisolid residue which was mixed thoroughly with 200 ml of water and 200 ml of chloroform. The chloroform layer was drawn off, and the aqueous layer was extracted with another 200-ml portion of chloroform. The combined organic phases were dried over anhydrous magnesium sulfate and concentrated under reduced pressure to yield a yellow-tinted oil, 2-*syn*-7-norbornanediol 7-*p*-toluenesulfonate (**10**) contaminated with the epimer **9**. The crude **10** was dissolved in a solution of 4 ml of

(34) For details of the Jones oxidation, see I. Heilbron, E. R. H. Jones, and F. Sondheimer, *J. Chem. Soc.*, 604 (1949).

acetone and 7.5 ml of glacial acetic acid. The resulting solution was cooled to 0° as 5.3 ml of chromic acid–acetic acid solution (prepared by dissolving 21 g of chromium trioxide in 17 ml of water and 35 ml of glacial acetic acid) was added dropwise with stirring over a duration of 16 min. The cold mixture was stirred for an additional 40 min, mixed with 200 ml of ether, washed with two 10-ml portions of water, three 20-ml portions of saturated sodium bicarbonate solution, and 10 ml of water, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to a yellow oil. Treatment of the oil with Girard's "T" reagent as above gave 0.438 g (11.7% over-all) of crude crystalline **4**. Recrystallization from hexane gave white crystals, mp 95.6–96.1°, which were identical in all respects with the material obtained by the first route.

syn-**7-Acetoxybicyclo[2.2.1]hept-2-one (16).** To a stirred solution of 1.87 g of **11** (contaminated with about 9% of **6**) in 10 ml of water was added 7 ml of 6 *M* chromic acid over a 15-min period and the temperature was maintained at 20–30°. Isopropyl alcohol (2 ml) was added and stirring was maintained for an additional 0.5 hr. The resulting dark mixture was extracted with three 15-ml portions of ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate, concentrated under reduced pressure to give crude **12**, which was dissolved in 10 ml of pyridine. This solution was cooled to 0° and 3.5 ml of acetic anhydride was added with stirring. The solution was allowed to warm and to stand at room temperature for 4.5 hr with additional stirring. The solution was again cooled to 0° and 10 ml of water was added dropwise. After 15 min of stirring, the solution was mixed with 90 ml of water and extracted with three 25-ml portions of ether. The combined extracts were washed with 15 ml of 20% sulfuric acid and with 15 ml of water, dried over anhydrous magnesium sulfate, concentrated under reduced pressure, and distilled to yield 0.673 g, bp 80–100° (1 mm). Vapor phase chromatography (15% didecyl phthalate on Chromosorb **P**) indicated a keto acetate–diacetate ratio of *ca.* 2:1, the *exo*-2-*syn*-7-diacetoxybicyclo[2.2.1]heptane–*exo*-2-*anti*-7-diacetoxybicyclo[2.2.1]heptane ratio being *ca.* 86:14. A portion of this material was purified by preparative vpc on the same column and by subsequent distillation to give an analytical sample, bp 78° (0.6 mm), n^{25}D 1.4725. The analytical sample consisted of a 93:7 ratio of **16**:**15**, as shown by vpc on a 100 ft × 1/16 in. capillary column coated with Carbowax 1500.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.28; H, 7.33.

anti-**7-Acetoxybicyclo[2.2.1]heptan-2-one (15).** A 5.240-g sample of pure **6** was converted to **15** by the same process as described above for the preparation of **16** to give 2.916 g of crude distilled product, bp 79–85° (0.4 mm). Vapor phase chromatography (15% didecyl phthalate on Chromosorb **P**) indicated a **15**–*exo*-2-*anti*-7-diacetoxybicyclo[2.2.1]heptane ratio of *ca.* 3:2, corresponding to a 25% yield of **15**. A portion of this material was purified by preparative vpc on the same column followed by subsequent distillation to give an analytical sample of **15**: bp 80° (0.7 mm); n^{26}D 1.4737.

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.48; H, 7.15.

Kinetics. Reagents. Anhydrous acetic acid was prepared by refluxing a solution of acetic anhydride and sodium acetate in glacial acetic acid for 24 hr and subsequent fractional distillation in a dry atmosphere. Standard sodium acetate in acetic acid (*ca.* 0.1 *M*) was prepared by the careful addition of anhydrous acetic acid to a solution of anhydrous sodium carbonate in acetic anhydride, such that *ca.* 1% acetic anhydride remained after the water of neutralization was removed, followed by refluxing in a dry atmosphere for 5 hr[35] (calculated to be 1.325 g of anhydrous sodium carbonate and 3.78 g of acetic anhydride diluted to 250 ml with anhydrous acetic acid). Standard perchloric acid in acetic acid (*ca.* 0.02 *M*) used in titrating acetolysis aliquots was prepared by the careful addition of 70% perchloric acid to a solution of anhydrous acetic acid and acetic anhydride, such that 1% acetic anhydride remained after the water was removed, followed by standing at room temperature for 12 hr. The molarity of the standard perchloric acid in acetic acid was determined by titrating an aliquot *vs.* potassium acid phthalate (primary standard) in anhydrous acetic acid using bromophenol blue as the indicator.

Acetic acid-O-*d* was prepared by the following procedure. A sample of acetic anhydride was fractionally distilled in a dry atmosphere. The first cut, bp 136–138°, was discarded. The second cut, bp 138–139°, was collected. A mixture of 20.00 g of deuterium oxide (Columbia Organic Chemical Co., Inc.), 103.98 g of acetic anhydride, and 0.663 g of anhydrous sodium carbonate was allowed to stand in a dry atmosphere for 58 hr and then refluxed for 2 hr. Nuclear magnetic resonance spectroscopy indicated 2.75–2.90% of protioacetic acid in the acetic acid-O-*d*. Titration of an aliquot with perchloric acid in acetic acid indicated 0.108 *M* sodium acetate content.

Kinetics. Procedure. The kinetic procedure followed was essentially that of Winstein and coworkers.[36] All rates were determined using an infinity titer, except in the case of **4** where extensive decomposition did not permit the determination of an infinity titer.

Product Analysis of the Acetolysis of 3. A solution of 1.227 g of **3** and 0.400 g of anhydrous sodium acetate in 25 ml of anhydrous acetic acid containing 5 drops of acetic anhydride was heated at 150–160° for 90 min. This solution was worked up and distilled as above to yield 0.466 g (63%) of an oil whose infrared spectrum was identical with that of the *anti*-acetate, **15**. Vpc (Capillary column, Carbowax 1500, 100 ft × 1/16 in.) established that no other volatile products were present. No *syn*-acetate, **16**, was observed. However, due to the almost identical retention times of **15** and **16**, it was impossible to establish the purity of **15** beyond 97%. An independent experiment showed that **16** did not epimerize to **15** under identical acetolysis conditions.

Product Analysis of the Acetolysis of 4. Because of the elevated temperatures required for the acetolysis of **4** numerous experimental difficulties were encountered. Extensive decomposition of both products and starting material occurred beyond *ca.* 10% reaction. Thus product analysis was carried out after *ca.* 5% reaction and the products identified represent the initially formed products.

Since product composition was determined on the basis of 5% reaction the purity of the starting tosylate was extremely critical. In particular, the presence of trace amounts of **3**, which would undergo acetolysis much faster than **4**, would greatly complicate the dependability of the results. This problem was removed by solvolytically removing any traces of **3** from the sample of **4** prior to the product determination.

A 250-ml round-bottomed flask fitted with a reflux condenser and drying tube was charged with a solution of 2.109 g of **4** in 100 ml of anhydrous acetic acid containing 0.85 g of anhydrous sodium acetate. The reaction mixture was refluxed for 3 days.[37] After cooling, the reaction mixture was poured into 1.5 l. of water and carefully neutralized with 250 g of sodium bicarbonate. The aqueous solution was extracted with three 500-ml portions of ether and the combined extracts were washed thoroughly with water and saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the solvent was removed on a flash evaporator. The residue was recrystallized several times from hexane to yield 0.571 g of pure *syn*-7-hydroxybicyclo[2.2.1]heptan-2-one *p*-toluenesulfonate (**4**), mp 94.5–95.2°.

A solution of 0.0148 g of **4**, free of any contamination by **3**, was dissolved in 1.0 ml of glacial acetic acid which was 0.09955 *M* in sodium acetate and the solution was sealed in an ampoule. The tube was heated to 205° for 4.5 hr. After cooling the ampoule was opened and the solvolysis mixture was poured into 2 ml of water and neutralized with 2.5 g of sodium bicarbonate. The slightly basic solution was extracted with two 10-ml portions of ether and the combined extracts were dried over anhydrous magnesium sulfate. Vpc of the ethereal solution showed five components. The major component was identified as *anti*-7-acetoxybicyclo[2.2.1]heptan-2-one (**15**) and the minor component was identified as *syn*-7-acetoxybicyclo[2.2.1]heptan-2-one (**16**). The three trace components were not identified although it was shown that none of these impurities was bicyclo[3.2.0]hept-2-en-4-one.

The ratio of **15** to **16** was 95:5. Based on the kinetics of the reaction it could be shown that the amount of **15** present corresponded to an 83% minimal yield calculated on the basis of consumed starting material.

Partial Acetolysis of *anti*-7-Hydroxybicyclo[2.2.1]heptan-2-one *p*-Toluenesulfonate (3) in Acetic Acid-O-*d*. Two samples of **3** were solvolyzed in acetic acid-O-*d*, each under different conditions. (a) A solution of 0.292 g of **3** in 8 ml of acetic acid-O-*d* buffered with 0.1 *M* sodium acetate was heated on a steam bath for several

(35) P. D. Bartlett and W. P. Giddings, *J. Am. Chem. Soc.*, **82**, 1240 (1960).

(36) S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

(37) This represents more than ten half-lives reaction time for **3**. Thus any 4 recovered from this acetolysis should be free of **3**.

hours, cooled, and worked up as before. (b) A solution of 0.431 g of **3** in 30 ml of acetic acid-O-*d* buffered with 0.1 *M* sodium acetate was heated at 110.00° for 75.5 min (39% reaction), cooled, and worked up as before. In each case the crude product was chromatographed through silica gel with benzene–ether to give an acetate fraction and a tosylate fraction. The acetate fraction was purified by preparative vpc (15% didecyl phthalate on Chromosorb P) in the case of a and by distillation (bp 75°, 0.25 mm) in the case of b. The infrared spectra of the acetates from a and b were identical, but were different from that of **15**. The tosylate fractions were purified by recrystallization from hexane (mp 97.0–98.0°). The infrared spectra of the tosylates from a and b were different from one another and from that for **3**; that from b was intermediate between that from a and that of **3**. The nmr pattern of the tosylate from b was identical with that of **3**, except that the intensity of a signal masked by the aryl methyl group was diminished. Mass spectral analyses indicated a monodeuterio percentage of 54% for the tosylate from a and 34% deuterium incorporation for the tosylate from b.

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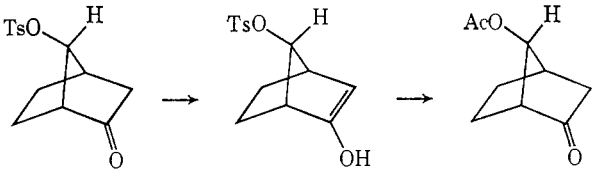
The Acetolysis of the Epimeric 3,3-Dimethyl-7-tosyloxybicyclo-[2.2.1]heptan-2-ones. The Interaction between Incipient Carbonium Ions and Neighboring Nonenolizable Ketones[1]

Paul G. Gassman[2] and Joseph M. Hornback[3]

Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received April 16, 1969*

Abstract: 3,3-Dimethyl-*syn*-7-tosyloxybicyclo[2.2.1]heptan-2-one and 3,3-dimethyl-*anti*-7-tosyloxybicyclo[2.2.1]-heptan-2-one have been prepared by nine and seven step synthetic sequences, respectively, starting with *dl*-camphor. The *anti* isomer underwent acetolysis *ca.* 20 times faster than the *syn* isomer and *ca.* six times faster than 7-tosyloxynorbornane. Whereas the *syn*-tosylate gave predominately a mixture of *syn*- and *anti*-7-acetoxy-3,3-dimethylbicyclo-[2.2.1]heptan-2-ones, the *anti*-tosylate gave the ring opened product, (Δ-2-cyclopentenyl)-2,2-dimethylacetic acid, as the only isolable compound. This behavior is contrasted with the corresponding acetolysis of *syn*- and *anti*-7-tosyloxybicyclo[2.2.1]heptan-2-one, where the enolizable character of the carbonyl function accounts for a drastically different rate comparison and product composition.

In the preceding paper[4] we discussed in detail the role of enolization in neighboring group participation of carbonyl functions. Although the small amount of enol present is generally not involved in ketone neighboring group participation,[5] we have found that in rigid bicyclic systems, where participation of the π and nonbonding electrons of the carbonyl group is stereochemically prohibited from interacting with the incipient carbonium ion center, this enol content can be the overriding factor in determining the rates and products of solvolysis. This point is dramatically illustrated by the case of the epimeric 7-tosyloxybicyclo[2.2.1]heptan-2-ones. Acetolysis of *anti*-7-tosyloxybicyclo[2.2.1]heptan-2-one (**1**) occurred 10^4 times faster than acetolysis of *syn*-7-tosyloxybicyclo[2.2.1]heptan-2-one (**2**). In addition **1** gave only *anti*-7-acetoxybicyclo[2.2.1]heptan-2-one (**3**), while **2** gave a mixture of **3** and *syn*-7-acetoxybicyclo[2.2.1]heptan-2-one (**4**). Solvolysis in acetic acid-O-*d* provided definitive evidence that **1** and **2** were solvolyzing by different mechanisms with enolization to **5** being the rate-determining step in the acetolysis of **1**. This example of rate and product dependence on the stereochemical relationship of the leaving tosylate function and the enolizable carbonyl group was instructive



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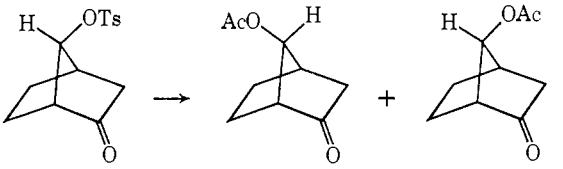
insofar as it unequivocally established the importance of considering the enol form in any study of carbonyl



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neighboring group participation. This unusual example raised the question of the chemical consequences of the stereochemical relationship between a leaving tosylate function and a nonenolizable ketone. The present paper describes the synthesis and solvolysis of model compounds which allow a critical evaluation of the interaction of nonenolizable ketones with incipient carbonium ion centers in rigid molecules.

(1) For a preliminary communication of part of this work, see P. G. Gassman and J. M. Hornback, *Tetrahedron Letters*, 1325 (1969).
(2) Alfred P. Sloan Research Fellow, 1967–1969.
(3) National Science Foundation Trainee, 1965–1968.
(4) P. G. Gassman, J. L. Marshall, and J. M. Hornback, *J. Am. Chem. Soc.*, **91**, 5811 (1969).
(5) D. J. Pasto and M. P. Serve, *ibid.*, **87**, 1515 (1965); D. J. Pasto, K. Garves, and M. P. Serve, *J. Org. Chem.*, **32**, 774 (1967); H. R. Ward and P. D. Sherman, Jr., *J. Am. Chem. Soc.*, **90**, 3812 (1968).