Unusually Facile Solvolysis of Primary Tosylates. A Case for Participation by the *N*-Nitroso Group[1]

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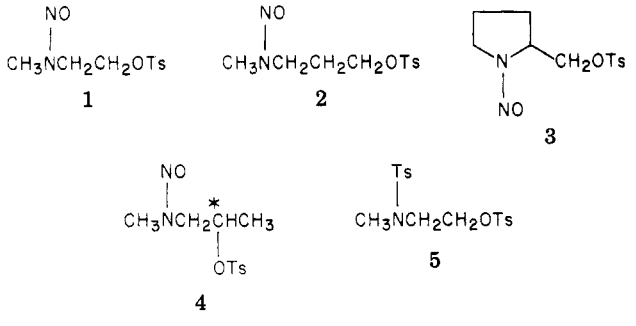
The acetolysis of the primary tosylates, *N*-methyl-*N*-nitroso-2-(tosyloxy)ethylamine (1) and *N*-methyl-*N*-nitroso-3-(tosyloxy)propylamine (2), gives the corresponding acetates in better than 80% isolated yields. The kinetic analysis of the acetolysis reactions indicated very rapid solvolysis. The activation parameters for 1 are $\Delta H^{\ddagger}$ = 17 kcal/mol and $\Delta S^{\ddagger}$ = −16.6 eu, and for 2 they are $\Delta H^{\ddagger}$ = 18.5 kcal/mol and $\Delta S^{\ddagger}$ = −21 eu. Acetolysis of the optically active secondary tosylate, (*S*)-*N*-methyl-*N*-nitroso-2-(tosyloxy)propylamine (4), resulted in net retention of configuration of the chiral reaction center. These data are best accounted for by invoking neighboring group participation by the *N*-nitroso function. The kinetic and stereochemical arguments were further bolstered by the isolation of the oxadiazolium ion **6a** from 1 in nonnucleophilic media.

Neighboring group effects are common in many nucleophilic reactions.[3] Various heteroatoms, unsaturated centers, and strained carbon–carbon σ bonds have been found effective as neighboring groups. The *N*-nitroso functionality, however, has not been implicated in that sense until very recently. We[4] postulated that the hydrolysis of α-ureidonitrosamines proceeded rapidly because the nucleophilic oxygen of the *N*-nitroso group interacted with the reaction center. Similarly, Harrington and coworkers[5] concluded that the rapid rates of hydrolysis of *N*-nitroso-3-(methylamino)propionitrile and *N*-nitroso-2-(methylamino)acetonitrile were due to the participation by the *N*-nitroso group.

In order to test the hypothesis of the *N*-nitroso group participation, we chose to examine a more clearly defined system. The present paper reports in some detail our investigation of the acetolysis of the β- and γ-(tosyloxy)nitrosamines 1–4. A preliminary study of the acetolysis of β-(tosyloxy)nitrosamines was communicated earlier.[6]



Results and Discussion

Synthesis. The preparations of tosylates **1**, **2**, **3**, and **5** were carried out in a straightforward manner. The corresponding nitrosamine alcohols, prepared from the amino alcohols by conventional nitrosation, were converted to the tosylates using the procedure of Schleyer.[7] Since the *N*-nitroso group also reacts with tosyl chloride, albeit slowly, the reaction mixtures were kept cold (0 to −15 °C) throughout the procedure. Tosylate **2** was crystallized with difficulty at −15 °C from ether. This was due partially to its low melting point (20–22 °C). As a consequence, the yield of this material was fairly low (25%), the losses having occurred during purification. The (tosyloxy)tosylamide **5** was prepared by the stepwise tosylation of the amino alcohol, first to form the tosylamide, which was then *O*-tosylated. The optically active (tosyloxy)nitrosamine **4** was prepared from ethyl L-(+)-lactate in four steps in

Scheme I

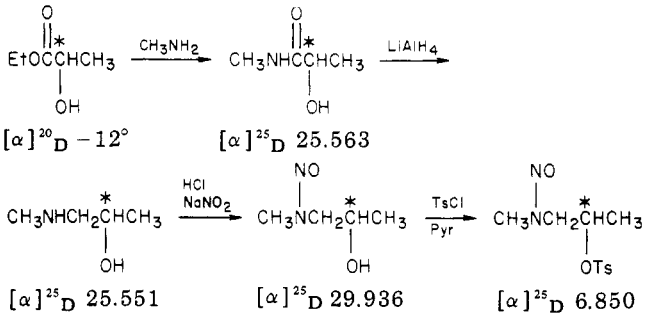


Table I. Acetolysis of *N*-Methyl-*N*-nitroso-2-(tosyloxy)ethylamine

k, $s^{-1} \times 10^4$	T, ±0.1 °C	no. of determinations
1.66 ± 0.05	15	3
2.90 ± 0.1	20	3
4.86 ± 0.2	25	3
9.03 ± 0.3	30	3
15.4 ± 0.6	35	4
16.6 ± 1.1	40	5

$\Delta H^{\ddagger}$ = 17.0 kcal/mol; $\Delta S^{\ddagger}$ = −16.6 eu.

Table II. Acetolysis of *N*-Methyl-*N*-nitroso-3-(tosyloxy)propylamine

k, $s^{-1} \times 10^4$	T, ±0.1 °C	no. of determinations
2.28 ± 0.05	60	3
3.17 ± 0.08	70	3
11.9 ± 0.6	80	3

$\Delta H^{\ddagger}$ = 18.5 kcal/mol; $\Delta S^{\ddagger}$ = −21 eu.

(1) Taken in part from the Ph.D. Thesis of Steven R. Koepke, University of Nebraska, 1978.
(2) NCI Frederick Cancer Research Center, P.O. Box B, Frederick, Md. 21701.
(3) B. Capon and S. P. McManus, "Neighboring Group Participation", Plenum Press, New York, 1976.
(4) C. J. Michejda, S. R. Koepke, and J. Mahaffy, *Tetrahedron Lett.*, 2573 (1976).
(5) S. K. Chang, G. W. Harrington, H. S. Veale, and D. Swern, *J. Org. Chem.*, **41**, 3752 (1976).
(6) C. J. Michejda and S. R. Koepke, *J. Am. Chem. Soc.*, **100**, 1959 (1978).
(7) P. v. R. Schleyer in "Reagents for Organic Synthesis", Vol. 1, L. F. Fieser and M. Fieser Eds., Wiley, New York, 1967, p 1180.

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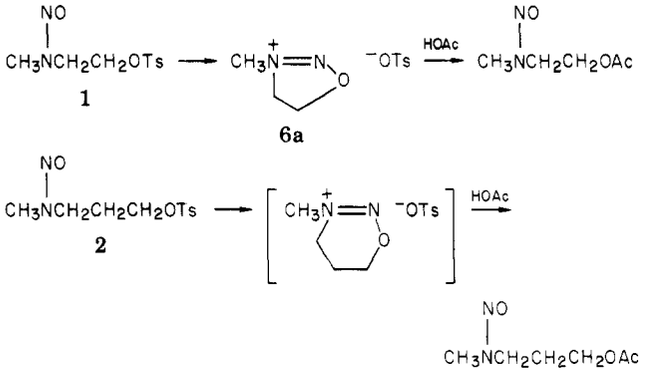
Table III. Acetolysis Rates of Primary Tosylates, ROTS

R	temp, °C	k, $s^{-1} \times 10^7$	ref
CH_3	75	8.52 ± 0.08	9
CH_3CH_2	75	7.39 ± 0.10	9
$(CH_3)_2CHCH_2$	75	2.30 ± 0.06	9
$(CH_3)_3CCH_2$	75	0.835	9
$PhCH_2$	25	26.1 ± 0.3	10

Scheme II



an overall yield of 50%, according to the sequence in Scheme I.

Acetolysis. The acetolyses were carried out in glacial acetic acid buffered with potassium acetate under a nitrogen atmosphere. For kinetic purposes, 3-mL aliquots of the solution were withdrawn and frozen at −78 °C. Titrations of the aliquots were carried out using a standard perchloric acid solution in glacial acetic acid. The reaction curves were linear to more than 80% completion. The acetolysis of tosylate **2** was carried out using the sealed ampule technique[8] because of the higher temperatures required to obtain a convenient rate of reaction.

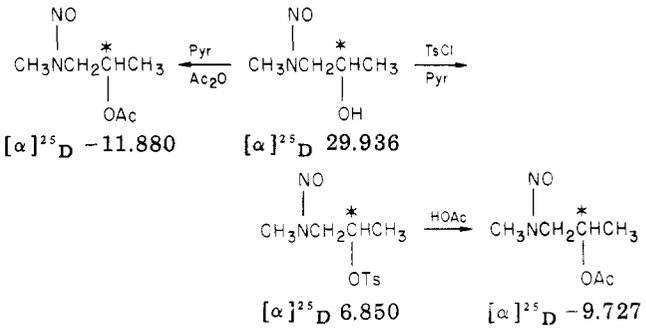
The acetolysis of the nitrosoprolinyl tosylate **3** was too rapid to measure by our method. It is estimated that the half-life of the reaction was ~30 s at 25 °C. The (tosyloxy)tosylamide **4** solvolyzed extremely slowly under these conditions, and no kinetic parameters for that compound were determined. Good kinetic data were obtained for tosylates **1** and **2**, and these are listed in Tables I and II. The products from both of the tosylates were the corresponding acetates, which were recovered in better than 80% yields from the kinetic runs. No other products were detected.

Considering the fact that compounds **1** and **2** are primary tosylates, the data presented in the tables represent extremely rapid rates of acetolysis. Table III[9,10] presents some representative data from the literature which illustrate the more "normal" rates for primary tosylate acetolyses.

It is interesting to note that even the very reactive benzyl tosylate solvolyzes some 200 times more slowly in acetic acid than tosylate **1**. The kinetic data strongly suggest that the acetolyses of tosylates **1** and **2** proceed with the neighboring group participation of the nucleophilic *N*-nitroso group, as shown in Scheme II.

It is interesting to compare tosylates **1**, **2**, and **3**. The extremely rapid rate of acetolysis of **3** is probably due to the relative ease with which the five atoms involved in the reaction reach the proper orientation with respect to one another. This is a consequence of the relatively rigid

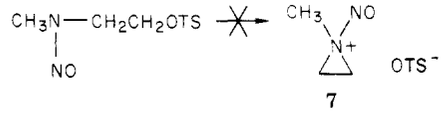
Scheme III



prolinyl system. In other words, the entropy of activation for that process is probably considerably more positive than that in the reactions of **1** and **2**. By the same token, the fact that the (tosyloxy)propylnitrosamine **2** has additional degrees of freedom in the carbon chain when compared with **1** requires that the acetolysis of **2** be considerably slower than **1**, the primary difference being in the more negative entropy of activation.

Further solid evidence for the participation of the *N*-nitroso function was provided by the acetolysis of the optically active nitrosamine tosylate, (*S*)-*N*-methyl-*N*-nitroso-2-(tosyloxy)propylamine (**4**). If the effect of the *N*-nitroso function were strictly an electronic one, and the reaction proceeded by direct displacement, then inversion of configuration would have been expected. If the reaction proceeded by the unlikely formation of the secondary cation, then primarily racemization would have occurred. If, on the other hand, the reaction proceeded by the intermediacy of the oxadiazolium ion similar to **6a**, then the stereochemical consequence would have been net retention, resulting from double inversion. The data shown in the following scheme indicate that indeed the third possibility is the correct one; i.e., the product exhibits substantial retention of configuration. The small amount of racemization (roughly 9%) might be due to direct displacement by the acetate. (Internal return, presumably involving the oxadiazolium ion, would not result in racemization.)

It is also interesting to note that the acetolysis of the (tosyloxy)tosylamide **5** was exceedingly slow under our conditions. No reaction was observed after 4 h at 25 °C. Since the nitrogen of the tosylamide should have similar nucleophilic properties to those of the amino nitrogen in tosylate **1**, the low reactivity of **5** indicates that the neighboring group effect in **1** is not via an aziridinium intermediate **7**. This was substantiated further by the



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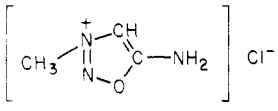
following results. When tosylate **1** was warmed in a nonnucleophilic solvent such as methylene chloride, the substance rearranged quantitatively to 4,5-dihydro-3-methyl-1,2,3-oxadiazolium tosylate, **6a**. The structure of this material was deduced from its ^1H NMR spectrum (see Experimental Section) which was similar to that of **1** except that the resonances were shifted downfield as a result of the positive charge. The IR spectrum of **6a** was transparent in the 1400–1800-cm^{-1} region, which indicates that the nitroso group had lost its identity. The ν_{NO} of bent X–NO species in inorganic complexes, for example, falls in the 1525–1690-cm^{-1} range.[11] The oxadiazolium salt **6a**

(8) S. Winstein, E. Grunwald, R. E. Buchler, and C. Hanson, *J. Am. Chem. Soc.*, **70**, 81 (1948).
(9) S. Winstein and H. Marshall, *J. Am. Chem. Soc.*, **74**, 1120 (1952).
(10) S. Winstein, E. Grunwald, and H. Jones, *J. Am. Chem. Soc.*, **73**, 2700 (1951).
(11) F. A. Cotton and G. W. Wilkinson, "Advanced Inorganic Chemistry", 3rd ed., Interscience, New York, 1972, p 716.

is remarkably stable in aqueous solution but reacts rapidly with a variety of nucleophiles[12] both at the original site of attachment of the tosyl group and also at the methyl. Acetate ion reacts exclusively at the β carbon. Compounds similar to **6a** have been reported previously; Daeniker and Druey[13] reported the formation of a related compound **8** by treatment of *N*-nitroso(2-methylamino)acetonitrile with HCl gas in nonaqeuous media. Interestingly, the next higher homologue, *N*-nitroso-(3-methylamino)propionitrile,



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failed to undergo the cyclization.[14]

The propyl tosylate **2** fails to form a stable cyclic salt in nonnucleophilic media. Prolonged heating in carbon tetrachloride solution results in the elimination of *p*-toluenesulfonic acid and the formation of the corresponding unsaturated nitrosamine. This material polymerizes readily in the presence of trace acid.[15]

Conclusion

The data presented in this paper strongly support the concept of neighboring group participation by the *N*-nitroso group, particularly when the leaving group is in the β-carbon. Participation also occurs when the leaving group is on the γ-carbon, but less efficiently.

The phenomenon of neighboring group participation by the *N*-nitroso group appears to be a general one, if the configuration of the molecule allows it. It is likely that it may also play a role in the biological activity of β-oxidized nitrosamines. This is particularly important because such nitrosamines are found in the environment[16] and may also be products of enzymatic oxidation of dialkylnitrosamines where the alkyl group is larger than methyl.[17]

Experimental Section

All melting points and boiling points are uncorrected. The infrared spectra were determined as solutions in chloroform using a Perkin-Elmer 621 grating spectrophotometer. The NMR spectra were determined in $CDCl_3$ unless otherwise indicated using Varian A-60-D and XL-100 spectrometers. The chemical shifts are reported in parts per million (ppm) downfield from the internal standard tetramethylsilane. High-resolution mass spectra were obtained using an AEI MS-5076 mass spectrometer equipped with an Incos 2010 mass spectrometer interface and a Nova 2 data system from Data General Corp. Elemental analyses were performed by Micro Tech Laboratories, Skokie, Ill. The optical rotations were measured on a Perkin-Elmer Model 141 automatic polarimeter.

***N*-Methyl-*N*-nitroso-2-hydroxyethylamine (9)** was prepared by the nitrosation of 1.0 mol of *N*-methyl-2-hydroxyethylamine with 1.1 mol of sodium nitrite and 1.5 mol of concentrated hydrochloric acid at 0 °C. The reaction mixture was added to 400 mL of 2-propanol and filtered, and all the solvent was evaporated. The product was chromatographed on silica gel using a 1:9 mixture of ethyl acetate and methylene chloride as elutant to yield 72.5 g (70%) of a pale yellow oil: bp 110–112 °C (1 mm) (lit.[18] bp 110.5–111.5 °C (1 mm)).

***N*-Methyl-*N*-nitroso-2-(tosyloxy)ethylamine (1)** was prepared using a modification of the procedure of Schleyer.[7] To a solution of 3 g (28.8 mmol) of **9** in 30 mL of pyridine which was cooled to 0 °C was added 11 g (57.6 mmol) of tosyl chloride. The solution was stirred at 0 °C for 0.5 h, and the flask was stored in a freezer at −15 °C overnight. The reaction was poured into a vigorously stirred mixture of 100 g of cracked ice and 200 mL of 1 M hydrochloric acid. After 10 min, the product crystallized and was isolated by vacuum filtration. After being dried under vacuum, the tosylate was chromatographed on silica gel using 1:9 ethyl acetate and methylene chloride and recrystallized three times from diethyl ether. The reaction yielded 2.36 g (29.5%) of the white crystalline material: mp 70–72 °C; ^1H NMR spectrum, δ 2.46 (s, 3, CH_3Ar), 3.02 (s, 3, CH_3N), 4.30 (s, 4, CH_2CH_2), 7.59 (m, 4, ArH).

Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.47; N, 10.85; S, 12.39. Found: C, 46.23; H, 5.35; N, 11.06; S, 12.45.

***N*-Methyl-*N*-nitroso-2-acetoxyethylamine (10)** was synthesized by adding a solution of 4.15 g (0.053 mol) of acetyl chloride in 15 mL of methylene chloride to a mixture of 5.35 g (0.053 mol) of triethylamine and 5 g (0.053 mol) of **9** in 25 mL of methylene chloride at −10 °C. After 2 h, the reaction mixture was washed six times with 20-mL portions of a saturated potassium carbonate solution and twice with 20-mL portions of a saturated sodium chloride solution. After the solution was dried over sodium sulfate, the product was chromatographed on silica gel using ethyl acetate and methylene chloride (1:9) as elutant, and the solvent was evaporated. The yield was 4.35 g (62%): ^1H NMR δ 2.04 (s, 3, OAc), 3.10 (s, 3, CH_3), 4.41 (s, 4, CH_2CH_2).

Anal. Calcd for $C_5H_{10}N_2O_3$: C, 41.08; H, 6.90; N, 19.17. Found: C, 41.28; H, 7.06; N, 19.05.

(*N*-Nitroso-2-pyrrolidine)methanol (11) was prepared by the nitrosation of 2-pyrrolidine methanol in a similar manner to **9**. The yield of the pale yellow oil was 79.6%: ^1H NMR δ 2.06 (m, 4, CCH_2CH_2C), 3.53 (m, 2, CH_2N), 4.42 (m, 2, CH_2O), 4.04 (m, 1, CH), 6.05 (m, 1, OH).

Anal. Calcd for $C_5H_{10}N_2O_2$: C, 46.13; H, 7.75; N, 21.53. Found: C, 45.91; H, 7.89; N, 21.74.

(*N*-Nitroso-2-pyrrolidine)methanol tosylate (3) was synthesized in a manner similar to that used for **1** except that the reaction mixture was poured into 300 g of cracked ice and distilled water rather than 1 M HCl. The yield was 2.52 g (42%): mp 51–53 °C; ^1H NMR δ 2.06 (m, 4, CH_2CH_2), 2.45 (s, 3, CH_3Ar), 3.53 (m, 2, CH_2N), 4.18 (m, 1, CH), 4.42 (m, 2, CH_2O), 7.56 (m, 4, Ar).

***N*-Formyl-3-hydroxypropylamine (12)** was prepared by reacting 35 g (0.46 mol) of 3-hydroxypropylamine with a threefold excess of ethyl formate. The reaction yielded 48.09 g (100%) of the formamide: ^1H NMR δ 1.75 (m, 2, CCH_2C), 3.49 (m, 4, CH_2CCH_2), 4.28 (s, 1, OH), 7.46 (s, 1, NH), 8.16 (s, 1, HCO).

***N*-Methyl-3-hydroxypropylamine (13)** was synthesized by adding a solution of 60 g (0.582 mol) of **12** in 50 mL of THF to a vigorously stirred suspension of 26.5 g (0.697 mol) of $LiAlH_4$ in 200 mL of THF at 0 °C. After addition, the reaction was heated at reflux for 2 to 3 h. The suspension was cooled to 0 °C, and 26.5 mL of water, followed by 80 mL of 10% sodium hydroxide, and again 26.5 mL of water were added to hydrolyze the mixture. The suspension was filtered, the precipitate was washed with THF, and the solvent was evaporated. The product was distilled (bp 91–93 °C [25 mm]) yielding 30.2 g (58%): ^1H NMR δ 1.72 (quin, 2, CCH_2C), 2.45 (s, 3, CH_3N), 2.85 (t, 2, CH_2N), 3.41 (s, 2, NH, OH), 3.80 (t, 2, CH_2O).

***N*-Methyl-*N*-nitroso-3-hydroxypropylamine (14)** was prepared in a manner similar to that used for **9** and **11**. The yield was 65.4%: ^1H NMR δ 1.98 (quin, 2, CCH_2C), 3.08 (s, 3, CH_3[syn]), 3.81 (s, 3, CH_3[anti]), 3.68 (t, 2, CH_2O[syn]), 4.29 (t, 2, CH_2O[anti]), 3.53 (t, 2, CH_2N[syn]), 4.18 (t, 2, CH_2N[anti]).

Anal. Calcd for $C_4H_{10}N_2O_2$: C, 40.65; H, 8.54; N, 23.72. Found: C, 40.82; H, 8.61; N, 23.49.

***N*-Methyl-*N*-nitroso-3-(tosyloxy)propylamine (2)** was synthesized by adding 6.1 g (0.032 mol) of tosyl chloride to a stirred solution of 3.85 g (0.032 mol) of **14** in 40 mL of dry pyridine at 0 °C. When solution was complete, the reaction was stored at

(12) The cyclic intermediate **6a** and the tosylate **1** react with thiols and amines as well as guanine and guanosine to give substitution products. These results will be reported shortly.

(13) H. Daeniker and J. Druey, *Helv. Chim. Acta*, **45**, 2426 (1962); H. Daeniker, *ibid.*, **47**, 33 (1964).

(14) S. K. Vohra, G. W. Harrington, and D. Swern, *J. Org. Chem.*, **43**, 1671 (1978).

(15) R. Kupper, unpublished data from this laboratory.

(16) P. A. Zingmark and C. Rappe, *Ambio*, **5**, 80 (1976); **6**, 237 (1977); T. Y. Fan, J. Morrison, D. P. Rounbehler, R. Ross, and D. Fine, *Science*, **196**, 70 (1977).

(17) F. W. Krüger, *Z. Krebsforsch.*, **79**, 80 (1973).

(18) N. N. Ogimachi and H. W. Kruse, *J. Org. Chem.*, **26**, 1642 (1961).

−15 °C overnight. The mixture was poured into 300 g of cracked ice and 1 M HCl with vigorous stirring. This solution was extracted with three 100-mL portions of methylene chloride. The extracts were combined and washed with two 100-mL portions of 1 M HCl and once with a 100-mL portion of ice water. The product was dried over sodium sulfate, filtered, treated with activated charcoal, and chromatographed on silica gel using methylene chloride as elutant. The product was recrystallized twice from dry ether at −15 °C yielding 2.23 g (25.1%): mp 20–22 °C; ^{1}H NMR δ 2.12 (quin, 2, CCH_2C), 2.46 (s, 3, CH_3Ar), 3.01 (s, 3, CH_3[syn]), 3.75 (s, 3, CH_3[anti]), 3.81 (t, 2, CH_2O[syn]), 4.20 (t, 2, CH_2O[anti]), 3.62 (t, 2, CH_2N[syn]), 4.10 (t, 2, CH_2N[anti]), 7.58 (m, 4, ArH).

Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.51; H, 5.98; N, 10.29; S, 11.75. Found: C, 48.66; H, 5.99; N, 10.37; S, 11.62.

***N*-Methyl-*N*-nitroso-3-acetoxypropylamine (15)** was prepared by adding 2 mL of acetic anhydride to 1 g (8.5 mmol) of **14** in 5 mL of pyridine at 0 °C. After 2 h, 50 mL of methylene chloride was added, and the solution was washed with five 50-mL portions of 1 M sodium carbonate and dried over sodium sulfate. The product was chromatographed on silica gel using methylene chloride as elutant yielding 0.89 g (65.6%): ^{1}H NMR δ 2.04 (s, 3, OAc), 2.16 (quin, 2, CCH_2C), 3.00 (s, 3, CH_3[syn]), 3.76 (s, 3, CH_3[anti]), 3.80 (t, 2, CH_2O[syn]), 4.14 (t, 2, CH_2O[anti]), 3.96 (t, 2, CH_2N[syn]), 4.28 (t, 2, CH_2N[anti]).

Anal. Calcd for $C_6H_{12}N_2O_3$: C, 44.98; H, 7.55; N, 17.49. Found: C, 45.08; H, 7.53, N, 17.37.

4,5-Dihydro-3-methyl-1,2,3-oxadiazolium tosylate (6a) was isolated by adding ether to a solution of 5 g (0.018 mol) of **1** in 50 mL of dry methylene chloride that had been heated at reflux for 2 h and cooled to room temperature. The product was recrystallized twice from methylene chloride and ether. The yield was 4.82 g (97%): mp 126–128 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.27 (s, 3, CH_3Ar), 4.18 (s, 3, CH_3), 5.13 (m, 4 H, CH_2CH_2), 7.35 (m, 4, ArH).

Anal. Calcd for $C_{10}H_{14}N_2O_4S$: C, 46.50; H, 5.47; N, 10.85; S, 12.39. Found: C, 46.72; H, 5.60; N, 10.79; S, 12.31.

***N*-Methyl-*N*-tosyl-2-hydroxyethylamine (16)** was synthesized by adding 63.4 g (0.33 mol) of tosyl chloride to a stirred solution of 25 g (0.33 mol) of *N*-methyl-2-hydroxyethylamine and 33.6 g (0.33 mol) of triethylamine at 0 °C in 100 mL of methylene chloride. The solution was stored overnight in a refrigerator. The organic layer was washed with 50 mL of 1 M HCl and two 100-mL portions of distilled water and dried over magnesium sulfate. After filtering the solution and evaporating the solvent, the resulting product was recrystallized from methylene chloride yielding 70.9 g (93%): mp 62–64 °C; ^{1}H NMR δ 2.46 (s, 3, CH_3Ar), 2.85 (s, 3, CH_3), 3.48 (m, 4, CH_2CH_2), 3.65 (s, 1, OH), 7.53 (m, 4, ArH).

Anal. Calcd for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.60; N, 6.11; S, 13.96. Found: C, 52.46; H, 6.75; N, 5.84; S, 14.23.

***N*-Methyl-*N*-tosyl-2-(tosyloxy)ethylamine (5)** was prepared in a manner similar to that used for tosylates **1** and **3**. The yield was 73%: mp 54–56 °C; ^{1}H NMR δ 2.48 (s, 6, CH_3Ar), 2.86 (s, 3, CH_3), 3.52 (m, 4, CH_2CH_2), 7.68 (m, 8, ArH).

Anal. Calcd for $C_{17}H_{21}NO_5S_2$: C, 53.25; H, 5.52; N, 3.66; S, 16.69. Found: C, 52.98; H, 5.63; N, 3.72; S, 16.88.

Kinetic Studies. Acetolysis of **1** was carried out in a thermostated (±0.1 °C), 125-mL, three-necked flask fitted with a mechanical stirrer and a nitrogen inlet (very slow stream). The flask was charged with 8.0 mL each of prewarmed stock solution of 0.16 M potassium acetate and 0.08 M tosylate in glacial acetic acid. The glacial acetic acid was distilled under nitrogen from a glacial acetic/acetic anhydride mixture through a 60-cm glass bead packed column. At intervals, 3-mL aliquots of the solution were withdrawn and immediately frozen in a dry ice–acetone bath. The aliquots were titrated with 0.0259 M perchloric acid in glacial acetic acid. The end points were determined potentiometrically. At least three runs were made at each temperature. The first-order rate plots were linear for at least 80% of the reaction. The rate constants were evaluated from a linear least-squares line.

Acetolysis of **2** was carried out by mixing 1.5 mL of each of the stock solutions of the tosylate (0.08 M) and potassium acetate (0.16 M) in glacial acetic acid in each of ten Pyrex tubes, which were then sealed. The tubes were placed in a thermostated oil bath (±0.1 °C) and were withdrawn at preset intervals and frozen in a dry ice–acetone bath. The titration of the contents of each tube was carried out using a standard 0.0358 M solution of perchloric acid in glacial acetic acid. The end points were determined potentiometrically, and the individual rate constants were calculated from a linear least-squares line. The first-order plots were linear for at least 90% of the reaction.

The product acetates were isolated from the acetolysis solutions by adding methylene chloride and washing the organic layer with six 20-mL portions of saturated potassium carbonate solution and drying over sodium sulfate. The products were then chromatographed on silica gel and were found to be spectroscopically identical with the standard samples. The isolation procedure produced the acetate in each case in greater than 80% yield. Ditosylate **6** yielded only the starting material. The acetate was the only product regardless of whether the product analysis was made with solutions containing the tosylates at the kinetic studies concentrations or at higher concentrations.

(*S*)-*N*-Methyllactamide (17). In a pressure bomb cooled to −70 °C was placed 22.0 g (0.186 mol) of ethyl L-(+)-lactate and 20.0 g (0.644 mol) of anhydrous methylamine. The bomb was then sealed and heated to 100 °C for 6 h at which point it was recooled, opened, and allowed to warm to room temperature, which allowed the excess amine to evaporate. The contents of the bomb were then taken up in ethanol and stripped of solvent in vacuo at 40 °C leaving 19.0 g (99%) of a heavy colorless oil: $[\alpha]^{25}_D$ −25.563° (*c* 10.171 in ethanol); ^{1}H NMR δ 1.39 (d, 3, CH_3), 2.81 (d, 3, CH_3N), 4.22 (q, 1, CHOH), 5.44 (bs, 2, OH, NH).

Anal. Calcd for $C_4H_9NO_2$: C, 46.59; H, 8.80; N, 13.58. Found: C, 46.66; H, 8.89; N, 13.50.

(*S*)-*N*-Methyl-2-hydroxypropylamine (18). The amide **17**, 19.0 g (0.184 mol), was added dropwise over 45 min to a solution of 10.0 g (0.286 mol) of lithium aluminum hydride in 500 mL of THF at 0–5 °C. Upon completion of the addition, the solution was heated to reflux for 6 h, cooled to 0–5 °C, and hydrolyzed with 10 mL of water, 30 mL of 10% NaOH, and 10 mL of water, successively. The resulting suspension was filtered, and the filter cake was washed with 2 × 100 mL of ether. The combined organic material was dried over anhydrous $MgSO_4$, filtered, stripped of solvent in vacuo at 25 °C, and distilled at 60–65 °C at 18 mm to yield 14.50 g (92%) of a colorless crystalline solid: mp 31.5–32 °C; $[\alpha]^{25}_D$ 25.551° (*c* 10.794 in ethanol); ^{1}H NMR δ 1.12 (d, 3, CH_3), 2.42 (s, 3, CH_3N), 2.50 (dd, 2, $-CH_2N$), 3.51 (s, 2, OH, NH), 3.85 (m, 1, CHOH).

Anal. Calcd for $C_4H_{11}NO$: C, 53.90; H, 12.44; N, 15.71. Found: C, 53.99; H, 12.59; N, 15.88.

(*S*)-*N*-Methyl-*N*-nitroso-2-hydroxypropylamine (19). This compound was prepared in the usual manner in 72% yield from **18** and rendered analytically pure by chromatography on silica gel (Fisher grade 923) with methylene chloride: $[\alpha]^{25}_D$ 29.936° (*c* 8.498 in ethanol); ^{1}H NMR δ 1.17 (d, 3, CH_3[syn]), 1.28 (d, 3, CH_3[anti]), 3.15 (s, 3, CH_3N[syn]), 3.89 (s, 3, CH_3N[anti]), 4.15 (m, 3, CH_2[anti], CHOH[syn,anti]), 3.72 (m, 2, CH_2[syn]).

Anal. Calcd for $C_4H_{10}N_2O_2$: C, 40.67; H, 8.53; N, 23.71. Found: C, 40.79; H, 8.77; N, 23.53.

(*S*)-*N*-Methyl-*N*-nitroso-2-(tosyloxy)propylamine (4). Compound **4** was prepared by the method of Schleyer[7] in 77% yield and recrystallized twice from pentane/chloroform (4:1) giving nearly colorless prisms: mp 80.5–81 °C; $[\alpha]^{25}_D$ 6.850° (*c* 7.810 in methylene chloride); ^{1}H NMR δ 1.34 (d, 3, CH_3), 2.46 (s, 3, CH_3Ar), 2.97 (s, 3, CH_3N), 4.29 (dd, 2, CH_2N), 4.94 (m, 1, CHOTs), 7.56 (m, 4, ArH).

Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29. Found: C, 48.22; H, 5.69; N, 9.98.

(*S*)-*N*-Methyl-*N*-nitroso-2-acetoxypropylamine (20). In a sealed vial, 2 g (0.0169 mol) of **10** was treated with an excess of acetic anhydride for 10 h at room temperature. The resulting red solution was poured into 50 mL of ice cold, 6 N HCl and quickly extracted with 5 × 20 mL of methylene chloride. The combined organic layers were then washed with 5% $NaHCO_3$, dried over anhydrous Na_2SO_4, and stripped of solvent in vacuo at 40 °C, leaving 2.4 g (94%) of a pale yellow solid: mp 36–37 °C; $[\alpha]^{25}_D$ −11.880° (*c* 10.261 in ethanol); saponification equivalent 160.272; mol wt 160.174; IR (CCl_4) 2995, 2950, 1750, 1465, 1245, 1045 cm^{-1}; ^{1}H NMR δ 1.18 (d, 3, CH_3[syn]), 1.30 (d, 3, CH_3[anti]), 2.03 (s, 3, CCH_3[syn,anti]), 3.08 (s, 3, NCH_3[syn]), 3.71 (m, 2, NCH_2[syn]), 3.83 (s, 3, NCH_3[anti]), 4.27 (m, 2, NCH_2[anti]), 5.22 (m, 1, CHOAc[syn,anti]).

Anal. Calcd for $C_6H_{12}N_2O_3$: C, 44.99; H, 7.55; N, 17.49. Found: C, 45.15; H, 7.49; N, 17.25.

Solvolysis of 4. In a vial were placed 1.0 g of **5**, 10 mL of HOAc, and 1.0 g of NaOAc; after sealing, the vial was heated at 60 °C for 6 h at which time the red solution was poured into 100 mL of CH_2Cl_2. The CH_2Cl_2 solution was then extracted repeatedly with saturated $NaHCO_3$. The neutral organic layer was then dried and stripped of solvent in vacuo leaving 357 mg (62%) of a dark red oil which was purified on a column of silica gel (Fisher grade 923) to give a pale yellow oil identical spectroscopically with **20**: $[\alpha]^{25}_D$ −9.729° (c 3.392 in ethanol).

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Registry No. **1**, 66398-63-8; **2**, 66398-65-0; **3**, 66398-64-9; **4**, 70377-71-8; **5**, 3559-06-6; **6a**, 70377-73-0; **9**, 26921-68-6; **10**, 70377-74-1; **11**, 68292-94-4; **12**, 49807-74-1; **13**, 42055-15-2; **14**, 70415-59-7; **15**, 70377-75-2; **16**, 59724-61-7; **17**, 60915-12-0; **18**, 70377-76-3; **19**, 70377-77-4; **20**, 70377-78-5; *N*-methyl-2-hydroxyethylamine, 109-83-1; 2-pyrrolidinemethanol, 498-63-5; 3-hydroxypropylamine, 156-87-6; ethyl formate, 109-94-4; ethyl L-(+)-lactate, 687-47-8.

Stereochemistry of the Photoinduced and Michael Addition of Methanol to Seven- and Eight-Membered 2-Cycloalkenones. The Effect of Methyl Substituents

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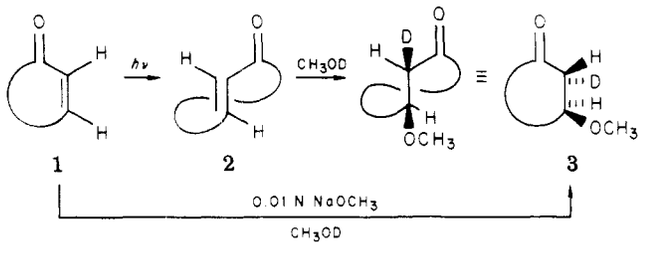
Irradiation of 2-methyl-2-cycloheptenone (**4**) or 2-methyl-2-cyclooctenone (**6**) in methanol gave only the corresponding *cis*-3-methoxy-2-methylcycloalkanones **5c** and **7c**, respectively, rationalized as a consequence of syn methanol addition to the trans enones. The isotope effect (CH_3OH/CH_3OD) for **4** was 2.0, appreciably less than the previously observed value for 2-cycloheptenone, suggesting that the 2-methyl substituent destabilizes the trans intermediate. Photoinduced methanol addition also occurred when the double bond had a methyl substitutent at C_3, but 2,3-dimethyl-2-cyclooctenone failed to add methanol photochemically. The base-catalyzed Michael addition of methanol to **4** and **6** gave a mixture of *cis*- and *trans*-3-methoxy-2-methylcycloalkanones, in contrast to the previously reported stereospecific additions to the unsubstituted 2-cycloalkenones. The acid-catalyzed addition of methanol to **4** gave a different cis-trans ratio than the base-catalyzed addition.

Strained trans seven- and eight-membered-ring 2-cycloalkenones, produced by irradiating the corresponding cis isomers,[1] react with alcohols and other nucleophiles to give Michael-type adducts.[2] By using CH_3OD as the nucleophile, we recently showed[3] that these reactions involve a regiospecific and stereospecific nucleophilic syn addition to the polarized, strained trans double bond (**2** → **3**). As part of a series of experiments designed to further probe the mechanistic details of this reaction, we also studied the base- and acid-catalyzed addition of CH_3OD to the cis ketones **1** and were surprised to find that the base-catalyzed Michael reaction is also stereospecific (i.e., **1** → **3**; **1** = 2-cycloheptenone, 2-cyclooctenone, and 2,3-benzo-2,6-cycloheptadienone).[3] Consistent with this observation, we found that the base-catalyzed deuterium exchange at C_2 in the corresponding 3-methoxycycloalkanones is also stereoselective, exchange being much faster for the proton trans to the methoxyl than for the corresponding cis proton. But the acid-catalyzed Michael addition, studied only with 2-cycloheptenone, was not stereoselective.



We decided that for at least two reasons it would be worthwhile to extend the above studies to cycloalkenones with methyl substituents on the carbon–carbon double bond. First, molecular models suggest that methyl substitution should, as a consequence of nonbonded interactions, increase the strain in the *trans*-2-cycloalkenones **2**. There is a question then of whether or not the trans isomers will be formed on irradiation and, if formed, whether they can be trapped. So far, there has been almost no systematic study of the effect of substitution on the stability and reactions of strained trans cycloalkenes. Second, it seemed important to determine whether the stereospecificity of the base-catalyzed Michael addition and deuterium exchange observed previously[3] is general. We report here our results on the effect which methyl substituents at C_2 and C_3 of 2-cycloheptenone and 2-cyclooctenone have on the outcome of the above reactions.

Results and Discussion

The Photoinduced Additions. Irradiation of 2-methyl-2-cycloheptenone (**4**) or 2-methyl-2-cyclooctenone (**6**) in methanol gave the *cis*-3-methoxy-2-methylcycloalkanones **5c** and **7c**, respectively. The cis stereochemistry

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