The Neighboring Sulfonium Group in Ester Hydrolysis. II[1]

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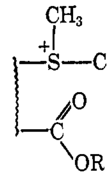
Abstract: Hydrolysis of methyl dimethylsulfonium acetate *p*-toluenesulfonate (**1**) at constant pH is shown to be first order in hydroxide ion and first order in ester in the range of pH 7 to 8.5. The entropy of activation is +17 ± 2.3 eu. Evidence is presented which suggests that the unusual value for $\Delta S^{\neq}$ involves a sulfonium hydroxide intimate ion pair.

In an earlier paper[1] we reported that cationic electrostatic catalysis to ester hydrolysis was very small in the system schematically illustrated by



for which a sulfonium sulfur atom was potentially capable of serving as an internal electrophilic catalyst during ester hydrolysis. That observation has been reinforced and generalized by the extensive data of Bruice[2] using other systems. In our earlier report we observed unusually large positive entropies of activation and suggested that the intervention of a ketene intermediate, the decomposition of which was monomolecular and rate controlling, could account for such an observation. The purpose of the present work was to test that suggestion.

Results and Discussion

A simple α-sulfonium ester capable of facile ylide formation was required for this study. Methyl dimethylsulfonium acetate *p*-toluenesulfonate (**1**), shown in Scheme I, satisfied that requirement. Hydrolysis of this ester in water at constant pH 7.0 was conducted and was monitored as described earlier.[1] The hydrolysis reaction could also be followed, although with less precision, by observing changes in the proton resonance spectrum of the ester in pH 7.0 buffered solution—a technique which also showed the appearance of inner salt **5** and methanol as the hydrolysis proceeded. The titrimetric rate constants were calculated as described previously[3] and are summarized as pseudo-first-order rate constants in Table I. A typical run is shown in Figure 1. From the data of Table I the reaction order with respect to hydroxide could be ascertained as one over the pH range 7 to 8.5, and the activation parameters were calculated from the graph shown in Figure 2. An activation energy of 22.5 ± 0.9 kcal/mol was calculated and corresponds closely to the values reported for methyl *o*- and *p*-dimethylsulfoniophenylacetates in our earlier studies,[1] and $\Delta S^{\neq}$ was found to be +17.7 ± 2.3 eu.[4] An increase in activation entropy over values determined for the sulfoniophenylacetates in the earlier work may reflect the change in water content of the solvent employed: 50% aqueous dioxane for the sulfoniophenylacetates to pure water in this case. The magnitude of E_a and the unusual sign of $\Delta S^{\neq}$ suggested a parallel between the hydrolysis pathway of the present and earlier case. By observing α-methylene proton exchange and hydrolysis simultaneously, using the proton resonance spectrum of **1** in buffered D_2O, it was found that the half-time for exchange, τ_{12}, was much less than 30 sec at room temperature and pH 7.0, leading to a ratio $k_{12}/k_{15} \gg 120$ (k_{12} is the specific rate constant for the reaction **1** → **2**). A value of $k_{12}/k_{15} > 1$ is a necessary but insufficient condi-

Scheme I

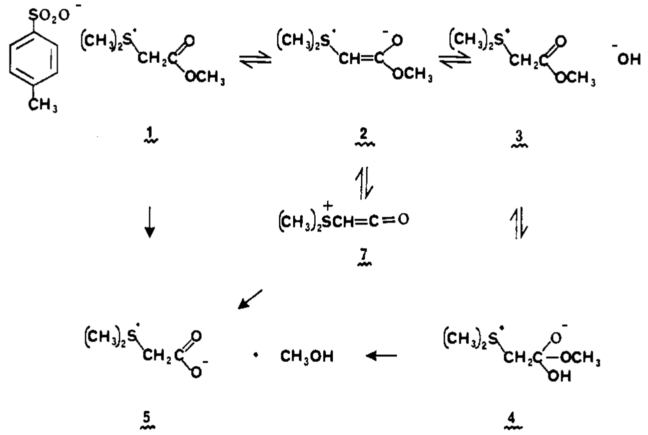


Table I. The Hydrolysis Rate of Methyl Dimethylsulfonium Acetate *p*-Toluenesulfonate in Water at Constant pH

Temp, °C	pH_{app}	$10^5 k_{15}$,[a] sec^{-1}	$10^5 k_{15}$,[a] sec^{-1} (av)
21.0	7.00	2.00	2.08 ± 0.08
		2.15	
37.6		20.70	20.40 ± 0.30
		20.10	
46.8		44.00	44.60 ± 0.40
		45.00	
		44.80	
58.5		164.0	164.0 ± 0.30
		164.0	
		163.0	
25.4	7.50	38.40	
	8.50	408.0	

[a] Pseudo-first-order rate constant for the reaction **1** → **5** in Scheme I.

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[1] Paper I: J. Casanova, Jr., N. D. Werner, and H. R. Kiefer, *J. Am. Chem. Soc.*, **89**, 2411 (1967). Leading references are cited therein.

[2] T. C. Bruice and B. Holmquist, *ibid.*, **89**, 4028 (1967).

[3] J. Casanova, Jr., and E. R. Weaver, *J. Chem. Educ.*, **42**, 137 (1965).

[4] Calculated from the expression $k_2 = (ek_BT/h)\exp(\Delta S^{\neq}/R)\exp(-E_a/RT)$. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

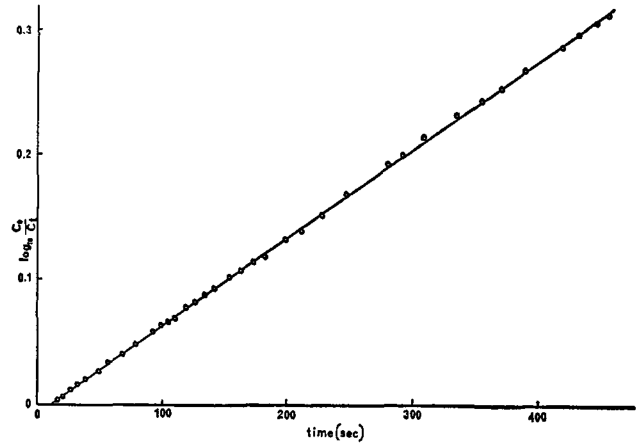

Figure 1. Log C_0/C_t vs. time for the hydrolysis of methyl dimethylsulfonium acetate p-toluenesulfonate in water at pH 7.00 and 58.5°.

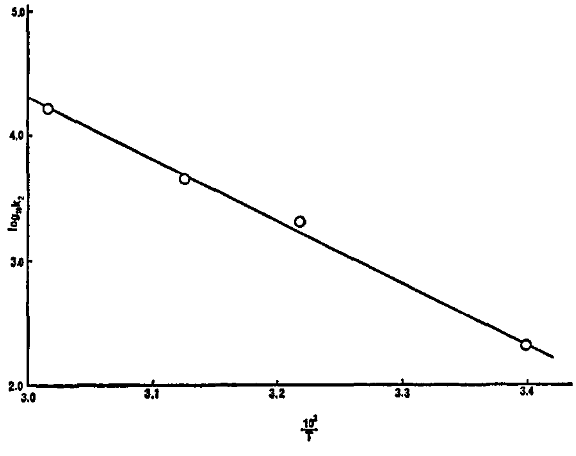

Figure 2. Log k_2 vs. $10^3/T$ for the hydrolysis of methyl dimethylsulfonium acetate p-toluenesulfonate in water at pH 7.00.

tion for the ketene intermediate in Scheme I to be a tenable proposal (**1** → **2** → 7 → **5**).

However, efforts to intercept a ketene directly met with failure. Preparation of **2** in dimethyl sulfoxide with sodium hydride followed by reaction with acenaphthalene[5] gave no isolable cyclobutanone products as evidence of cycloaddition of a ketene.[6] A similar result was observed using cyclohexene which gave no isolable cyclobutanone products.[5] In this latter instance, evidence was obtained for cyclopropane formation *via* the addition of ylide **2** to α,β-unsaturated esters produced from **1** and **2**. This reaction has been extensively studied.[7,8] A cycloaddition reaction[9] or a Diels–Alder reaction of **2** with butadiene, the latter reaction which could produce phenol, were sought but not found. Moreover, pure **2**[7b] was chemically rather stable in a scrupulously anhydrous environment even in the presence of a highly polar medium such as dimethyl sulfoxide, or in the presence of very concentrated aqueous base. If ketene formation from ylide **2** is the rate-controlling step in ester hydrolysis, it might be anticipated that in concentrated aqueous base in which ylide formation is complete the hydrolysis rate should be greatest. It is perhaps noteworthy that ethyl (dimethylsulfuranylidene)acetate is stable in strong aqueous base,[7c] and none of its many reactions are easily accommodated by a ketene intermediate.[7e] Cyclopropanization of acenaphthalene by the ylide, as evidence for a carbene, was similarly unsuccessful.

Results which are obtained from changes in the proton resonance spectra upon hydrolysis of some of the species shown in Scheme I are, however, very informative. Pure **2**[7b] when hydrolyzed in unbuffered D_2O formed inner salt **5** very rapidly ($\tau_{25} \ll 30$ sec), fully exchanged at the α-methylene group. Under the same conditions inner salt **5** did not undergo α-methylene proton exchange rapidly. A similar result was obtained with **2** in D_2O buffered at pH 7.0. However, **2**, when placed in D_2O to which 1.1 equiv of p-toluenesulfonic acid had been added, gave **1**, often with some hydrolysis, but in a mixture which did not undergo further measurable hydrolysis during many hours at room temperature. The α-hydrogen nmr signal in ester **1**, which had been prepared by hydrolysis of **2** in this way, showed only 0.35 ± 0.07 atom of residual α-hydrogen, over a wide range of conditions in the order of mixing the reagents and variation in dilution and temperature at the time of mixing. Under similar conditions of concentration and temperature, ester **1** did not suffer α-hydrogen exchange at a measurable rate. The results of hydrolysis of ylide **2** are shown in Table II. A value of 0.333 atom of residual α-hydrogen is expected for equilibrium distribution of α-hydrogen atoms between one molecule of protio ylide **2** and one molecule of D_2O if complete equilibrium is reached in such a

Table II. Incorporation of Deuterium from D_2O into Dimethylsulfonium Carbomethoxymethylide

Sample, mmol	p-$CH_3C_6H_4$-SO_2OD, mmol	D_2O, mmol	Cosolvent	Mode of mixing	Atom % α-H
0.83	0.90	25.0	None	*a*	0.24
1.36	1.50	25.0	None	*a*	0.34
1.10	1.10	25.0	None	*b*	0.32
1.05	1.15	27.0	Tetrahydrofuran	*c*	0.39
1.15	1.29	28.0	Tetrahydrofuran	*d*	0.35
1.01	1.11	27.0[e]	Tetrahydrofuran	*f*	0.69

[a] D_2O-TsOD solution was placed onto the frozen ylide and the mixture allowed to warm to 0° with stirring. [b] D_2O-TsOD solution was added rapidly to the ylide at 25° and the resulting solution frozen quickly. [c] Ylide **2**, dissolved in 5.0 ml of anhydrous tetrahydrofuran, was added to D_2O-TsOD over 4 min with good stirring. [d] Same as *c*, except ylide 2 was dissolved in 10.0 ml of tetrahydrofuran. [e] 1:1 mol ratio of H_2O-D_2O. [f] Same as *d*, except hydrolysis medium was 1:1 H_2O-D_2O.

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(5) (a) R. N. Lacey, "Advances in Organic Chemistry, Methods and Results," Vol. II, Interscience Publishers, New York, N. Y., 1960, pp 213–265; (b) G. Quadbeck, "Newer Methods of Preparative Organic Chemistry," Vol. II, W. Foerst, Ed., Academic Press, New York, N. Y., 1963; (c) J. D. Roberts and C. M. Sharts in "Organic Reactions," Vol. 12, A. C. Cope, Ed., John Wiley & Sons, New York, N. Y., 1962, p 27; (d) R. N. Lacey in "The Chemistry of Alkenes," S. Patai, Ed. John Wiley & Sons, New York, N. Y., 1964, p 1173; (e) C. D. Hurd and R. D. Kimbrough, Jr., *J. Am. Chem. Soc.*, **82**, 1373 (1960).

(6) V. J. Hruby and A. W. Johnson, *ibid.*, **84**, 3586 (1962). See also F. Serratosa and J. Quintana, *Tetrahedron Letters*, 2245 (1967).

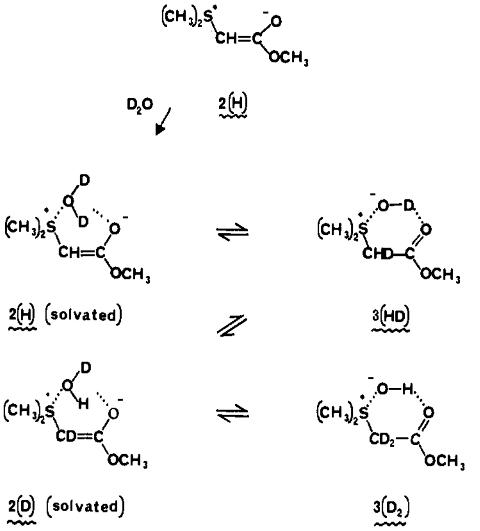
(7) (a) G. B. Payne, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 9–15, 1967, Abstract S158; (b) J. Casanova, Jr., and D. A. Rutolo, Jr., *Chem. Commun.*, 1224 (1967); (c) G. B. Payne, *J. Org. Chem.*, **32**, 3351 (1967); (d) for a comprehensive review, see A. W. Johnson; "Ylid Chemistry," Academic Press, New York, N. Y., 1966, pp 304–362; (e) G. B. Payne, *J. Org. Chem.*, **33**, 1285, 3517 (1968).

(8) (a) B. M. Trost, *J. Am. Chem. Soc.*, **89**, 138 (1967); (b) E. J. Corey and M. Jantelat, *ibid.*, **89**, 3912 (1967).

(9) See, however, W. T. Brady and H. R. O'Neal, *J. Org. Chem.*, **32**, 2704 (1967).

system. Hence, these data constitute persuasive evidence for sulfonium ester–hydroxide intimate ion pairing (see **3**, Scheme I), the integrity of which is preserved for a sufficient time to permit complete equilibration of the vinylic proton of ylide **2** with a specific solvent molecule of D_2O. That intimate ion pairing should be reasonable in this system is supported by the studies of Hogen-Esch and Smid[10] on ion pairing of fluorenyl salts in which they showed that with large, poorly solvated cations ion pairing was at a maximum. Such cage effects in water are well documented.[11] The equilibration is depicted in Scheme II. Leakage from the intimate sulfonium–hydroxide ion pair to a solvent-separated ion pair can occur from **3**(HD) or **3**(D_2), but the present experimental result suggests that the cage equilibration reaction is much more rapid than leakage out of the cage. Hydroxide ion destruction in a medium of high acidity should be a diffusion-controlled process[12] and would lead to a mixture of precisely the stoichiometry of **1** and of demonstrable stability toward further α-hydrogen exchange. The variety of conditions employed for hydrolysis of ylide **2**, all leading to the same resulting incorporation of deuterium, diminish greatly the possibility that local high hydroxide concentration in an inhomogeneous medium can be invoked as a rationale to account for the present result.

Scheme II



There is, intrinsic to the ion pair suggested in Scheme II, an attractive rationale to account for the unusually favorable $\Delta S^{\neq}$ of ester hydrolysis in the present case (**1** → **5**, Scheme I) and in the cases reported earlier.[1] Since formation (and destruction) of ylide **2** is much more rapid than ester hydrolysis (*vide infra*), the sulfonium–hydroxide intimate ion pair is a logical intermediate precursor to hydrolysis as well as exchange. Compound **3**, formed in a rapid equilibrium which precedes rate-controlling hydroxide ion attack at the ester carbonyl group, is already quite favorably disposed in space for the transformation to intermediate **4**. The reaction **3** → **4** is anticipated to be entropically more favorable than normal bimolecular saponification reactions.[13] Moreover, Doering[14] has ascertained that the entropy of activation for sulfur ylide formation is nearly zero, a phenomenon which he attributes to release of solvent upon ylide formation. The present rationale does not demand the intervention of any new mechanistic pathway, such as that involving a ketene. The demonstrated stability of the ethyl ester of **2** in the presence of very high hydroxide concentration,[7c] an observation which we have substantiated and extended to the methyl ester of **2**, strongly suggests that **1** is intermediate in the hydrolysis process, since ester **1**, with a pK_a of approximately 8,[15] should be completely converted to **2** under these conditions. Hence, if decomposition of **2** to **1** were favorable, it should occur best under these circumstances. Repression of ester hydrolysis rate by the presence of an α-carbanion has been suggested by Sacher and Laidler.[16]

Experimental Section

Methyl S-Methylmercaptoacetate. To a cooled solution of 11.5 g (0.5 g-atom) of sodium dissolved in 150 ml of methanol was added a solution of 46 g (0.5 mol) of methyl mercaptoacetate in 50 ml of methanol. To this solution was added, dropwise, with stirring and cooling, 63 g (0.5 mol) of dimethyl sulfate. The mixture was refluxed for 30 min and cooled, and a solid appeared. The solid was removed by filtration and washed with 50 ml of anhydrous methanol. The combined filtrate and washing were evaporated *in vacuo* to remove methanol. The residual oil was extracted into ether and washed with 0.2 *N* sodium hydroxide. The dried ether solution was concentrated and the residual oil distilled at 65–68° (18 mm) (lit.[17] bp 60–62° (20 mm)) to give 31 g (52%) of a colorless liquid. The infrared ($\bar{\nu}_{C=O}$ 1740 cm^{-1}) and proton resonance spectra (*cf.* Table III) were consistent with the assigned structure.

Methyl Dimethylsulfonium Acetate *p*-Toluenesulfonate (1). A solution of 25 g (0.21 mol) of methyl S-methylmercaptoacetate and 41 g (0.22 mol) of methyl *p*-toluenesulfonate was heated at 100° for 3 hr. The resulting viscous oil was dissolved in 90 ml of anhydrous acetone and 25 ml of ether was added. A crystalline mass formed upon adding a seed to this solution at −10°. Recrystallization of the solid from acetone–ether gave 49.7 g (77%) of a hygroscopic white solid, mp 74.5–76.5°. The infrared ($\bar{\nu}_{C=O}$ 1740 cm^{-1}) and proton resonance spectra (*cf.* Table III) were consistent with the assigned structure.

Anal. Calcd for $C_{12}H_{18}O_5S_2$: C, 47.02; H, 5.92. Found: C, 46.80; H, 6.21.

Kinetic Procedures. The constant pH hydrolysis procedures employed here have been described in detail.[1] The sample **1** (61.3 mg, 0.2 mmol) was dissolved in 50.0 ml of 0.10 *N* sodium *p*-toluenesulfonate, the latter to maintain nearly constant ionic strength throughout the reaction. Sodium hydroxide (0.100 *N*) was employed for titration. Least-squares rate constants were computed automatically.[3]

Nmr Procedures. Normally, 1 mmol of the sample to be studied was dissolved in 25 mmol (0.25 ml if molar concentration was not critical) of solvent as quickly as possible (*ca.* 5 sec) and the solution

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[10] (a) T. E. Hogen-Esch and J. Smid, *J. Am. Chem. Soc.*, **88**, 307 (1966); (b) L. L. Chan and J. Smid, *ibid.*, **90**, 4654 (1968); (c) for an excellent discussion of ion pairing see E. M. Kosower, "An Introduction to Physical Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1968, pp 352–382.

[11] E. F. Caldin, "Fast Reactions in Solution," John Wiley & Sons, Inc., New York, N. Y., 1964, p 282.

[12] M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964).

[13] M. L. Bender, R. D. Ginger, and J. P. Unik, *J. Am. Chem. Soc.*, **80**, 1044, (1958); A. Fischer, W. J. Mitchell, G. S. Ogilvie, J. Parker, J. E. Packer, and J. Vaughan, *J. Chem. Soc.*, 1426 (1958); E. Tommila, A. Nurro, R. Muren, S. Merenheimo, and E. Vuorinen, *Suomen Kemistilehti*, **32B**, 115 (1959); K. J. Laidler and D. Cheu, *Trans. Faraday Soc.*, **5b**, 1026 (1958); J. E. Earley, C. E. O'Rourke, L. B. Clapp, J. O. Edwards, and B. C. Lawes, *J. Am. Chem. Soc.*, **80**, 3458 (1958); A. Moffat and H. Hunt, *ibid.*, **81**, 2082 (1959); S. Sarel, L. Tsai, and M. S. Newman, *ibid.*, **78**, 5420 (1956); T. C. Bruice and G. L. Schmir, *ibid.*, **79**, 1663 (1957); G. L. Nolan and E. S. Amis, *J. Phys. Chem.*, **65**, 1556 (1961).

[14] W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **77**, 521 (1955).

[15] M. Caserio, private communication.

[16] E. Sacher and K. J. Laidler, *Can. J. Chem.*, **42**, 2404 (1964).

[17] W. R. Kirner, *J. Am. Chem. Soc.*, **50**, 2446–55 (1928).

Table III. The Chemical Shifts of Compounds **1**, **2**, and **5**

		Chemical shift, ppm[a]						
Compound	Solvent	CH_3S-	$CH_3\underset{+}{S}<$	$-CH_2-$	$-CH{=}C<$	$-CO_2CH_3$	CH_3OH	
$CH_3SCH_2CO_2CH_3$	Neat	2.16		3.22		3.68		
1	$CDCl_3$		3.10	4.75		3.40		2.32
1	D_2O		2.86	4.30		3.75		2.25
2	$CHCl_3$		2.77		2.87	3.55		
2[b]	D_2O		2.93	4.18			3.32	
1[c]	D_2O		2.89	3.90			3.35	
1[d]	D_2O		2.87	Absent		3.73		2.25
1[e]	D_2O		2.77[f] 2.89[f]	Absent		3.75	3.27	2.26

[a] Relative to internal tetramethylsilane when organic solvent was employed, and to external tetramethylsilane when water was employed. [b] Immediately gives **5** plus methanol. [c] Phosphate buffer, pH 7.0, α-hydrogen exchange complete in less than 3 min. [d] Carbonate–bicarbonate buffer, pH 9.78, α-hydrogen exchange complete in much less than 30 sec. Hydrolysis detectable after *ca.* 5 min. [e] Sodium carbonate, 0.1 *N*, pH 10.8, α-hydrogen exchange complete in much less than 30 sec. Hydrolysis detectable after *ca.* 2 min. [f] The 2.77-ppm peak is due to $CH_3S^+<$ in **5**, and the 2.89-ppm peak is due to $CH_3S^+<$ in **1**.

transferred to an nmr tube. The sample was rapidly frozen in liquid nitrogen and maintained at −200° until immediately before measurement of the spectrum. The manipulation usually required less than 20 sec to time of freezing. Samples of ylide **2**, when nonaqueous solvents were employed, were degassed and sealed in nmr tubes under vacuum. See Table III for specific details and values of chemical shifts. In all cases the correctness of peak assignment was verified by the addition of the appropriate authentic sample at the end of each study.

Methyl (Dimethylsulfuranylidene)acetate (2). To a solution of 0.677 g (17.3 g-atoms) of potassium in 20 ml of anhydrous *t*-butyl alcohol was added 5.04 g (16.5 mmol) of carefully dried sulfonium ester **1**. The alcohol was lyophilized from the solution under high vacuum and the residual oily solid extracted with several portions of dichloromethane under nitrogen. The dichloromethane was filtered and removed under vacuum and the resulting oil (1.70 g, 77%) molecularly distilled at 50° (5×10^{-4} mm) to give a clear viscous oil, which, upon cooling, crystallized (mp 19–21°). The infrared ($\bar{\nu}_{C=C}$ 1630 cm^{-1}) and proton resonance spectrum (*cf.* Table III) are in accord with structure **2**.[7b,c] The ylide **2** could also be conveniently prepared in 10–100-g quantities in aqueous solution by the method of Payne.[7c] Details of the proton resonance spectrum of **2** and its temperature dependence[18] are reported elsewhere.[7b]

Dimethylsulfonium Acetate.[19] Ylide **2** (100 mg) was dissolved in 1 ml of H_2O. An nmr spectrum of this solution taken immediately showed ylide **2** and ester **1** to be entirely absent and replaced by a spectrum which consisted of four lines, δ 2.93 (s, 6 H), 3.38 (s, 3 H), 4.18 (s, 2 H), and 4.80 ppm (s). The 3.38-ppm peak was due to methanol and the 4.80-ppm peak was due to water (see Table III). The solution was evaporated to dryness and dried at 60° (0.1 mm).

Ketene and Carbene Trapping Experiments. A. Ylide 2 with Butadiene.[9] Ylide **2** (0.445 g, 3.7 mmol) in 2 ml of anhydrous dimethyl sulfoxide and butadiene (100 ml, gas, 760 mm, 25°, 4.5 mmol) were sealed in evacuated tube and heated for 50 hr at 70°. The tube was opened and the residue refluxed briefly with excess 1 *N* sodium hydroxide. The acidified ether extract yielded a small amount of yellow oil which showed no infrared characteristics of phenol, and failed to give a color with alcoholic ferric chloride. A similar experiment using 2.00 g of **2** and 8.15 g of butadiene in 2 ml of benzene shaken at room temperature for 2 days and worked up in a similar manner gave only 5 mg of acidic ether-soluble material, which failed to give a positive ferric chloride test and showed no infrared characteristics of phenol.

B. Ylide 2 with Cyclohexene. Equimolar quantities of dimsylsodium[20] and tosylate ester **1** in dimethyl sulfoxide were mixed with a large excess of chromatographically pure cyclohexene and refluxed for 21 hr. The neutral pentane-soluble fraction yielded a chromatographically complex mixture of self-condensation products of the ylide,[7b,c] containing neither ketonic materials nor the *exo* or *endo* isomer of methylnorcarane-7-carboxylate when compared to authentic samples of the latter.[21]

C. Ylide 2 with Acenaphthalene. Prolonged heating at 100° of ylide **2**, prepared from **1** using dimsylsodium[20] in dimethyl sulfoxide, with a large excess of acenaphthalene failed to give any ether-soluble neutral aromatic carbonyl compounds as measured by infrared after careful column chromatography.[5]

Acknowledgments. The authors are grateful to the National Science Foundation and California State College, Los Angeles Faculty Grants and Research Committee, for financial support of this research.

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(21) Samples of the corresponding acids were kindly provided by Professor C. Foote, University of California, Los Angeles, Calif.