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Original Scientific Paper

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

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Z- and *E*-2-carbomethoxy-3-(methylenedimethylsulfonio)-bicyclo-[2.2.2]octane *p*-toluenesulfonate (**8z** and **8e**, respectively) were synthesized and saponified at constant pH to study the effect of the neighboring sulfonium group on the rate of reaction. Rates and activation parameters are very similar for both isomers, lending support to the theoretical prediction that charge-dipole and charge-charge separation in both isomers is not significantly different, and that the carbonyl-dipole vector is nearly normal to a line connecting it with the sulfonium sulfur atom.

INTRODUCTION

The presence of a polar substituent commonly produces changes in ionization constants for organic acids or changes in reactivity for organic esters or other derivatives. Such polar substituent effects can be due to delocalized resonance effects or to localized effects acting through bonds (inductive effect) or through space (electrostatic field effect). The relative importance of the inductive effect and the electrostatic field effect has been the subject of a number of investigations but continues to be of some controversy.[2,3] Ideal systems in which to determine the relative importance of these effects would have rigid fixed stereochemistry allowing variation in the number of links

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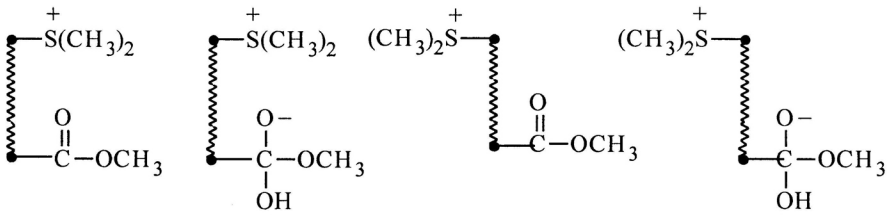
between the polar substituent and the reactive site as well as predictable variation in the stereochemistry with a fixed number of links. The pioneering work of Roberts and coworkers[4] utilized the rigid structure and variable polar substituents in 4-substituted bicyclo[2.2.2]octane-1-carboxylic acids. The rigid framework of a series of 3-substituted 3-phenylnorbornene-2-carboxylic acids enabled Beugelmans-Verrier[5] and coworkers to study the effects in a precise geometry with a fixed linkage.[6] In enzymatic reactions, both theoretical and experimental studies indicate that electrostatic effects are of paramount importance.[7]

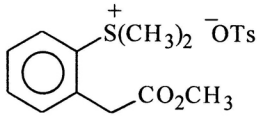
The extensive distribution of sulfonium compounds in biological systems[8] adds to the theoretical interest of such a phenomenon. The catalytic influence may be exhibited through reversible covalent bonding or through noncovalent interactions. Current evidence suggests that the importance of field effects outweigh those of inductive effects of polar substituents,[9] although some evidence to the contrary has appeared.[10]

Some time ago we sought to establish whether electrophilic catalysis by a neighboring sulfonium group would induce a rate increase in alkaline ester hydrolysis.[11] Intramolecular electrophilic catalysis in alkaline ester hydrolysis was proposed for the hydroxyl proton four decades ago[12] and is thought to be of the general acid type. A neighboring sulfonium sulfur atom could provide charge-dipole stabilization to the carbonyl group of an ester which is appropriately oriented and held in juxtaposition to it (a), or provide charge-charge stabilization for the hydrolytic intermediate in $B_{AC}2$ intermediate (b) compared to isomers in which the carbonyl group is remote (c) and the intermediate similar distal from the sulfonium group (d). The operation of either effect will serve to decrease the activation energy for hydrolysis involved, although the charge-charge effect is expected to predominate.[13]



In earlier studies methyl 2- and 4-dimethylsulfoniophenylacetate *p*-toluenesulfonates (**1** and **2**) were prepared, and the kinetics of their saponification compared. A small rate-enhancing effect of the sulfonium group was observed ($k_{ortho}/k_{para} = 5.2$), but a firm conclusion regarding the results was

rendered ambiguous by an unusually large positive entropy of activation which suggested the intervention of a different hydrolytic mechanism – possibly elimination/addition *via* a ketene.[11,14]



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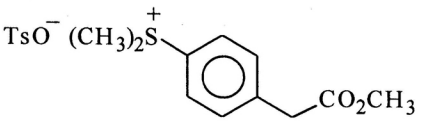

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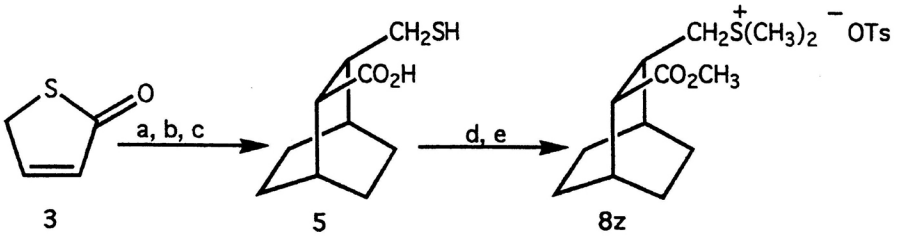
RESULTS

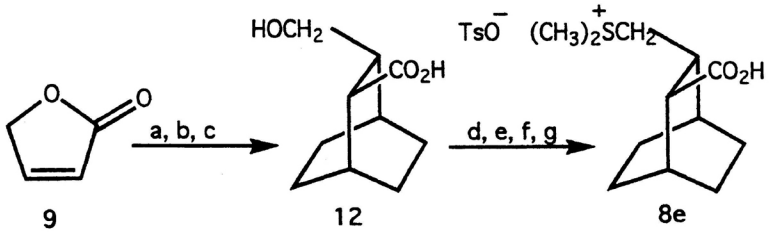
To extend this study to a system for which the mechanistic uncertainties inherent to the study of **1** and **2** were absent, we prepared and measured the alkaline saponification kinetics of *Z*- and *E*-2-carbomethoxy-3-(methylene-dimethylsulfonio)bicyclo[2.2.2]octane *p*-toluenesulfonate (**8z** and **8e**, respectively). These isomeric esters, which we expected would differ principally in the proximity of the carboxyl and sulfonium centers, could provide a test of the effect of the neighboring sulfonium-sulfur atom on ester saponification rates. The preparation of these compounds is shown in Charts I and II.

Compounds **8z** and **8e** were hydrolyzed titrimetrically in aqueous 0.10 N potassium tosylate by the introduction of very small increments of 0.01 N potassium hydroxide automatically at a rate such as to maintain the pH constant at a preset value. Rate data were evaluated to extract pseudofirst order rate constants for the hydrolysis of each isomer. Details of the kinetic procedure and data treatment are given in the Experimental section. The kinetic results are summarized in Table I. Comparable data pairs from Table I each reveal that the ratio of rate constants, $k(z)/k(e) = 1.3$. While the hydrolysis of **8e** was first order to six halflives ($R = 1.00$), the hydrolysis of



(a) 1,3-cyclohexadiene; 145°. (b) H_2, Pd/C, 25°;
(c) CH_3OH/NaOH, then H^+; (d) CH_2N_2/ether, 25°; (e) CH_3OTs, 50°

Chart I



(a) 1,3-cyclohexadiene, 145°; (b) H_2, Pd/C, 25°; (c) NaOH, heat, then H^+; (d) CH_2N_2/ether, 25°; (e) $(C_6H_5)_3P$, Br_2, 25°; (f) CH_3SNa, 55°; (g) CH_3OTs, 50°

Chart II

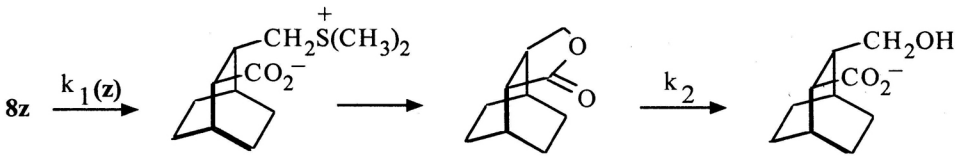
the *cis* isomer, **8z**, was complicated by a subsequent reaction, the intramolecular S_N2 ring closure to the γ-lactone, **17**. Although the ring-closure was not kinetically detectable by hydroxide consumption, the ring-opening reaction which followed was an hydroxide-consuming step. The overall process was then a series of pseudo-first order reactions which could be readily dissected kinetically.[15]

TABLE I

The hydrolysis rates of 2-carbomethoxy-3-(methylenedimethylsulfonio)-bicyclo[2.2.2]octanes *p*-toluenesulfonates in 0.1 N potassium tosylate at constant pH

Compound	Temp./°C	pH_{app}[a]	$10^4k_1/sec^{-1}$	10^4k_1 avg/sec^{-1}
8z	32.48 ± 0.02	11.70	3.80	3.84 ± 0.03
			3.87	
8e			3.05	2.99 ± 0.06
			2.94	
8z	40.20 ± 0.02	11.45	6.20	6.10 ± 0.10
			6.01	
8e			4.65	4.76 ± 0.11
			4.87	
8z	50.0 ± 10.02	11.18	12.49	11.94 ± 0.45
			11.39	
8e			8.60	8.64 ± 0.05
			8.69	
8z	50.01 ± 0.02	10.90	5.29	5.42 ± 0.13
			5.54	
8e			4.48	4.34 ± 0.15
			4.19	

[a] Calculated from pH = K_w − pOH. K_w has been corrected for temperature.



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The nature of the subsequent reactions of **8z** could be readily ascertained by following changes in the ^{1}H-NMR and observing the formation and destruction of intermediates. At 50.01 °C the pseudo first order rate constant for lactone ring opening was 3.75×10^{-4} sec^{-1}. The ratio of 3.2 for ester saponification/lactone saponification rates was approximately constant for all temperatures in this study. Activation parameters for the $B_{AC}2$ reaction of **8z** and **8e** were calculated, as were the second order rate constants. Calculation of the rate constants confirmed first order dependence on hydroxide concentration. The activation parameters are shown in Table II.

TABLE II

Activation parameters for the hydrolysis of 2-carbomethoxy-3-(methylenedimethylsulfonio)bicyclo[2.2.2] octanes *p*-toluenesulfonates at pH = 11.18 and 323.17 K

Compound	E_a/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
8z	48.6	−161
8e	47.8	−166

The values of activation energy are within experimental error the same for the isomeric esters. Both values of entropy of activation are large and negative, characteristic of bimolecular reactions in general and of saponification of hindered esters in particular.[16] Such small differences between isomer hydrolysis rates do not invite elaborate theoretical speculation as to the source, but do provide a vehicle for the examination of models designed to calculate the magnitude of the field effects.

DISCUSSION

To assess the field effect of the positive sulfonium sulfur atom on the rate of hydrolysis, both the charge-dipole stabilization of the reactant and the charge-charge stabilization of the reactive transition state (as modeled by the intermediate) need to be considered. If W_e* is the charge-charge elec-

trostatic free energy term in the transition state, and W_m^* is the charge-dipole free energy term in the reactant as defined for the Westheimer-Kirkwood-Tanford (WKT)[17,18] model, then the energy difference for the two isomers is:

$$\Delta\Delta G_E^* = \Delta G_E^*(Z) - \Delta G_E^*(E)$$

in which

$$\Delta G_E^*(Z) = W_e^*(Z) - W_m(Z)$$

$$\Delta G_E^*(E) = W_e^*(E) - W_m(E)$$

According to the WKT model (the terms have the usual definitions):

$$W_e^* = \frac{q_1 q_2}{D_E R} \quad \text{and} \quad W_m = \frac{q\,|m|\cos z}{D_E R^2}$$

If we assume that the charge-charge electrostatic free energy term for the intermediate is the same as that for the transition state ($W_e^{int} = W_e^*$) then since:

$$\Delta\Delta G_E^* = -k_B\, T \ln\frac{k_z}{k_e}$$

and

$$\frac{k_z}{k_e} = \exp\left(-\frac{W_e^{int}(Z) - W_m(Z) - W_e^{int}(E) + W_m(E)}{k_B T}\right)$$

Despite configurational differences between the *Z* and *E* isomers, force field calculations of the molecular geometry (11) of **8z** and **8e**, supported by careful examination of CPK models, indicate the most favorable geometry of both the starting esters and the intermediate oxy-anions have the sulfur atom almost equidistant from the centers of the carbonyl dipole in the isomeric esters and from the oxy-anion nucleus in the stereoisomeric intermediates.

Although examination of CPK models indicated that a significant stereochemical difference between **8z** and **8e** was possible, subsequent careful analysis of force field calculations of the molecular geometry[17] of **8z** and **8e** failed to support the initial conjecture. Despite configurational differences between the *Z* and *E* isomers, the most favorable geometries of both starting

esters and their intermediate oxy-anions are such that critical atoms for field effect interactions are located at similar distances from each other. The situation is further complicated by the observation that molecular mechanics calculations suggests the presence of many conformers of similar energy. A population analysis of conformers for the most abundant conformers is shown in Table III.

TABLE III

Calculated Energy Minima for Conformations of **8z** and **8e**

Ground State (sulfonio ester)			
8z(a)		**8e**(a)	
Energy minimum (Kcal/mol)	Mol fraction	Energy minimum (Kcal/mol)	Mol fraction
25.58	0.1934	22.69	0.2940
25.60	0.1871	22.76	0.2646
25.80	0.1340	22.79	0.2489
25.86	0.1213	23.56	0.0690
25.94	0.1061	23.68	0.0565
26.97	0.1010	24.02	0.0320
Intermediate (oxy anion)			
8z(b)		**8e**(b)	
Energy minimum (Kcal/mol)	Mol fraction	Energy minimum (Kcal/mol)	Mol fraction
–1.20	0.4447	–4.43	0.5157
–1.06	0.3522	–4.40	0.4439
–0.46	0.1296	–2.87	0.0403
–0.12	0.0735	–	–

Molecular overcrowding results from the neighboring substituents, which occupy secondary positions on the bicyclooctyl ring, and from hydrogen atoms on the proximal ethano ring bridge. Such overcrowding forces the $-CH_2S^+(CH_3)_2$ substituent into an orientation in which it is directed away from the carbonyl substituent. This feature is illustrated in Chart III. The structural representations of Chart III lead to a mole fraction weighted average of separation distances and orientations shown in Table IV.

Examination of models based on lowest energy conformational prediction suggests that approach of the reagent by hydroxide ion to the carbonyl carbon atom will be similarly and seriously hindered on the side proximal to the substituent for both isomers **8z** and **8e**, and moderately hindered by the ring

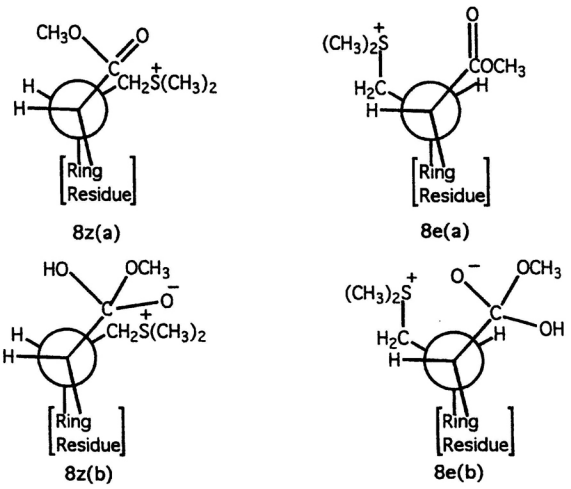


Chart III

hydrogens on the distal side. Large and similar steric hindrance to the approach of reagent would produce the unusual large and similar entropies of activation, reported in Table II.[16] Theoretical structure calculations at the semi-empirical level (AM1) for the most abundant ground state conformations of **8z** and **8e** fully support the molecular mechanics calculations, and are shown in Chart IV.

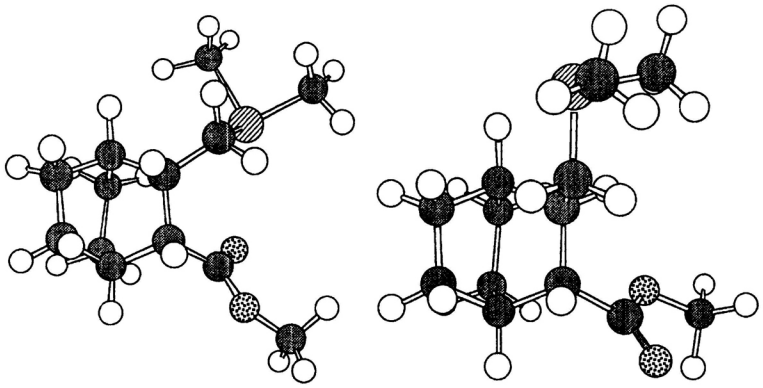
TABLE IV

Weighted average charge-dipole and charge-charge separations and orientation in most stable conformers related to **8**

	8z(a)[a]	**8z**(b)[b]	**8e**(a)[a]	**8e**(b)[b]
Distance *R*/pM	473	492	496	492
Angle ζ/degrees[c]	99	–	83	–

[a]Separation in pM between a line connecting the sulfur nucleus and the center of the carbonyl dipole. [b]Separation, in pM, between the sulfur nucleus and the oxy anion nucleus, determined by molecular mechanics force field calculations. [c]The angle between lines connected the positive charge with the center of the dipole and the dipole vector, measured from the negative end of the dipole.

Using the structural data of Table III, it is possible to evaluate the relative reaction rates of **8z/8e** in terms of the Kirkwood-Westheimer field effect model[18] as modified by Tanford.[19] Although field effect calculations have been largely directed to acidity in carboxylic acids[9e,f,20] the calculations



8z **8e**

Chart IV

should also be applicable here. The electrostatic contribution to the free energy of activation difference between **8z** and **8e** can be estimated by calculations of the electrostatic contributions to the electrostatic free energy terms W_m for charge-dipole interaction of the reactants (**8z**(a) and **8e** (a)) and W_e for charge-charge interaction of the intermediates (**8z**(b) and **8e**(b)). This approach is summarized in Table V.

TABLE V

Electrostatic energy of terms of the $B_{ac}2$ reaction if **8z** and **8e** as estimated by the KWT ellipsoidal cavity model

Species	λ_o[a]	μ/D	cos z	D_E[b]	$\Delta W/2.3kT$[c]
8z(a)[d]	1.423	1.78	–0.156	10.6	+0.29
8z(b)[e]	1.407			49.3	–1.00
8e(a)	1.403	1.78	0.122	11.1	–0.19
8e(b)	1.407			49.3	–1.00

[a]Calculated using $d = 1.0$ for charge-charge and $d = 1.5$ for charge-dipole species, Ref. 11a. [b]Reference 13a, Table 1. [c]Dimensionless energy term. [d]Charge-dipole parameters for ground state electrostatic interaction. [e]Charge-charge parameters for tetracoordinated intermediate electrostatic interaction.

The electrostatic free energy terms of Table IV lead to a calculated rate ratio, $k_z/k_e = 0.82$ at 298 K, which is comparable to the experimentally observed ratio. It is noteworthy that the unfavorable relationship between the carbonyl dipole and the charge in **8z** results in the prediction of a small rate

inhibiting effect in the ground state. Such an observation is not without precedence. In both isomers the predicted angle ζ is close to 90°, virtually negating any charge-dipole contribution from this species. Steric differences between isomers **8z** and **8e** are not large, and particularly in the case of the intermediates, charge-charge separation is calculated by MM2 to be identical. KWT calculations for electrostatic free energy contributions to the $B_{AC}2$ rates of esters in which significantly closer approach of charges and dipoles are possible suggest that a large rate enhancement should be observed for such cases, encouraging the study of other rigid model compounds.

EXPERIMENTAL

Reagents

Pentane was purified by distillation over potassium hydroxide and stored over molecular sieve. Benzene was distilled from sodium and stored over molecular sieve. Anhydrous alcohols were freshly prepared by distillation over sodium. Tetrahydrofuran, boron trifluoride etherate and diglyme were purified according to the procedures described by Fieser[22] and stored under nitrogen in serum capped flasks. The diglyme purification is treacherous because the initial drying with calcium hydride is not efficient and the subsequent dehydration with lithium aluminum hydride must be done with extreme caution to prevent an explosion. Dioxane was distilled over calcium hydride. Pyridine, methyl *p*-toluenesulfonate, dimethyl sulfate, and thionyl chloride were distilled prior to use.

Kinetic Procedure

The hydrolysis cell was 100 ml in capacity. A Corning calomel fiber junction reference electrode, a Corning triple purpose Ag/AgCl internal pH electrode and buret delivery tube were inserted in the cell which was equipped with airtight connections at all outlets. Measurements of pH were made with a Corning model 12 research pH meter with a 1 : 10 expanded scale for measurement to 0.005 pH unit. Titration was performed with a Sargent model C automatic constant rate burette. The constant rate burette was controlled and its operation recorded as described previously.[11] Hydrolysis was conducted in 0.10 N potassium *p*-toluenesulfonate with a pH adjusted to 6.3 (50 °C). The titrant was 0.1036 N ± 0.0001 potassium hydroxide.

*Z-4-Mercapto-2-butenoic Acid, γ-Thiolactone (**3**)*

Thiolactone **3** was prepared according to Frisell[23] from thiophene *via* 2-bromothiophene and *t*-butyl perbenzoate. 2-Bromothiophene, prepared according to VanDer Plas[24] was obtained in 44 % yield. Using *N*-bromosuccinimide instead of bromine a yield of 77% was reported.[25] *t*-Butyl perbenzoate was made from *t*-butyl hydroperoxide according to Milas:[26] NMR (CCl_4) δ/ppm: 7.64 (dt, 1.0 H, J = 6.0, 2.5 Hz, ring =CH), 6.29 (dt, 1.0 H, J = 6.0, 2.5 Hz, ring =CH), 4.15 (t, 2.0 H, J = 2.5 Hz, ring CH_2); (lit.[27] IR and UV published).

exo/endo-*Z-Carboxy-3-(mercaptomethylene)bicyclo-[2.2.2]oct-5-ene, γ-Thiolactone (4)*

1,3-Cyclohexadiene (6.53 g, 81.6 mmol), 2-hydroxythiophene **26** (7.38 g, 73.8 mmol) and 5 ml of benzene were combined and heated in a pressure vessel at 145 °C for 2 days to give a yellow oil after cooling and opening the pressure vessel (76 %). Distillation of the residual oil at 90–120 °C (0.01 mm) gave 8.81 g (66 %) of thiolactone **4**, a clear colorless oil which crystallized and was suitable for the next step without further purification. Recrystallization with pentane/ether gave white crystals: m.p. 45.0–45.2 °C; IR (CCl_4) ν_{max}/cm^{-1}: 5.90 m (s) (C=0); NMR (CCl_4) δ/ppm: 6.43–6.03 (complex dd, 1.9 H, ring =CH), 3.72–3.23 (m, 1.0 H, CH_2S), 3.23–2.87 (m, 1.9 H, CH_2S and ring H2), 2.87–2.47 (m, 2.8 H, ring H1, H3 and H4), 1.85–0.85 (complex q, 4.1 H, ring CH_2). Two additional recrystallizations gave white plates m.p. 50.0–50.2 °C after prolonged drying.

Anal. Calcd. for $C_{10}H_{12}OS$: C 66.61, H 6.76, S 17.80. Found (analysis I): C 67.18, H 6.73; found (analysis II): C 66.45, H 7.28, S, 18.35.

Z-2-Carboxy-3-(mercaptomethylene)bicyclo[2.2.2]-octane, γ-Thiolactone (5)

Compound **4** in methanol was hydrogenated over Pd/C (10%) at 49 psi for 2 h in the presence of several drops of conc. sulfuric acid. The reaction mixture was neutralized with sodium bicarbonate, extracted with ether, washed with water, aqueous sodium bicarbonate and 10 ml of water. The ethereal solution was dried, filtered and evaporated leaving a yellow oil of crude saturated thiolactone **5** (87%). The crude oil was chromatography on alumina in pentane to give white crystals. Recrystallization from pentane/ether gave white crystals (64%) m.p. 62–65 °C with an apparent phase change at 56 °C: IR (CCl_4) ν_{max}/cm^{-1}: 5.89 m (C=0); NMR (CCl_4) δ/ppm: 3.82–3.38 (m, 0.8 H, CH_2S), 3.38–3.00 (m, 1.1 H, CH_2S), 3.00–2.33 (m, 0.9 H, ring H2), 2.63 (m, 1.0 H, ring H2), 2.23–1.87 (br s, 1.2 H, ring H3), 1.87–0.98 (m of 1 peak, 9.0 H, ring CH_2 and H4). One more crystallization and prolonged drying in vacuum gave m.p. 69.8–70.0 °C.

Anal. Calcd. for $C_{10}H_{14}OS$: C 65.87, H 7.75, S 17.60; found: C 67.18, H, 8.32, S 17.53.

Z-2-Carboxy-3-(mercaptomethylene)bicyclo[2.2.2]-octane (6)

Thiolactone **6** in methanol under nitrogen was stirred with solid sodium hydroxide at room temperature for 11 h and a deep green solution resulted. The methanol was removed *in vacuo* and a slight excess of cold conc. hydrochloric acid was added. The yellow solution was diluted with water, extracted and the ether washed with saturated aqueous sodium chloride. The burgundy red ether extract was dried and concentrated leaving 95% of crude **6**, an orange solid. This material was suitable for the next step in the synthesis without further purification. A small amount of crude **6** was recrystallized from pentane/ether giving orange crystals. Another small portion of crude **6** was chromatographed using alumina/pentane to give pink crystals which were recrystallized from pentane/ether giving pale yellow opaque crystals of **6**, m.p. 91–92 °C; IR (CCl_4) ν_{max}/cm^{-1}: 5.86 (C=0), 2.8–4.2 m (s, broad, (O–H); NMR (CCl_4) δ/ppm: 11.93 (s, 1.0 H, CO_2H), 3.30–2.35 (m, 3.0 H, CH_2S and ring H2), 2.35–2.02 (m, 1.0 H, ring H3), 2.02–0.52 (m of 1 peak, 11.0 H, ring CH_2, H1 and H4, and SH).

Z-2-Carbomethoxy-3-(thiomethylmethylene)bicyclo[2.2.2]-octane (7)

The thioether was prepared according to an earlier procedure.[11] Metallic sodium (1.93 g, 84.0 mmol, 1.6 equiv.) was added rapidly to 100 mL of methanol. After the reaction had subsided, an orange solution of thiol **6** in methanol (10.38 g, 51.9 mmol, 1.0 equiv.) was added over a 5 min period. Dimethyl sulfate (6.72 g, 53.4 mmol, 1.0 equiv.) was then added by dropping funnel over a 5 min interval to the dark green reaction mixture. The solution was refluxed for 30 min. Filtration and removal of the methanol *in vacuo* left a red salt. An ice cold solution of 6.62 ml conc. hydrochloric acid/100 ml water (a 5% excess) was used to acidify the red salt. The resulting solution was extracted with water and ether. The ethereal layer was washed with saturated aqueous sodium chloride. A twofold excess of ethereal diazomethane (*ca.* 160 mmol)[28] was added in portions to the red ethereal solution until the evolution of nitrogen ceased. Excess diazomethane was decomposed with a few drops of acetic acid, and the orange etheral solution was dried, filtered and the ether removed, leaving 10.18 g of a red oil and crystals. The red oil with crystals was diluted with pentane and filtered. Evaporation of the solvent gave 9.39 g of crude **7**, as a red oil. The red oil was rapidly chromatographed on alumina using pentane. Early fractions were combined and distilled [b.p. 100–116 °C (0.02 mm)] to give a bright orange-yellow oil, 7.69 g, homogeneous by glpc. Rechromatography on alumina using pentane gave **7** as a clear yellow oil; the oil was suitable for the next step without further purification. An analytical sample of **7** was obtained by careful column chromatography followed by distillation, b.p. *ca.* 80 °C (0.01 mm)] using a short path distillation tube. Material was collected as a clear colorless oil: IR (CCl_4) ν_{max}/cm^{-1}: 5.76 m (C=0); NMR (CCl_4) δ/ppm: 3.59 (s, 3.0 H, CO_2CH_3), 2.97–2.77 (m, 0.6 H, ring H2), 2.62 (dd, 2.4 H, J = 8.0 Hz, CH_2S), 2.50–2.05 (m, 1.3 H, ring H3), 2.00 (s, 3.0 H, SCH_3), 1.98–0.85 (m, 9.7 H, ring CH_2, H1 and H4).

Anal. Calcd. for $C_{12}H_{20}O_2S$: C 63.12, H, 8.83, S 14.04; found: C 63.33, H, 8.81, S 13.89.

Z-2-Carbomethoxy-3(methylenedimethylsulfonium)-bicyclo[2.2.2]-octane Tosylate (8z)

Methyl thioether (0.436 g, 1.91 mmol, and freshly distilled methyl *p*-toluenesulfonate (0.496 g, 2.67 mmol, 1.4 equiv.) were heated at 50 °C for 22 h. The mixture solidified. The solid was triturated with ether and the white solid which remained was isolated by filtration. The solid was recrystallized from dioxane and methanol at 60 °C. The solid **8z** was dried thoroughly in vacuum. The yield of **8z** was 0.502 g (63 %): m.p. 141–142 °C; IR (KBr) ν_{max}/cm^{-1}: 5.78, ($CHCl_3$) 5.8 m (C=0); NMR ($CDCl_3$) δ/ppm: 7.70 (d, 2.0 H, J = 8.0 Hz, ArH), 7.12 (d, 2.0 H, J = 8.0 Hz, ArH), 3.93–3.50 (br d, 2.0 H, J = 4.5 Hz, CH_2S^+), 3.60 (s, 3.0 H, CO_2CH_3), 3.07 (d, 6.0 H, J = 4.5 Hz, $(CH_3)_2S^+$), 2.77 (m, 1.0 H, ring H2), 2.57–1.95 (m, 1.0 H, ring H3), 2.33 (s, 3.0 H, $ArCH_3$), 1.88 (br s, 1.0 H, ring H1), and 1.75–0.83 (m, 9.0 H, ring CH_2 and H4).

An analytical sample of **8z** was obtained by one recrystallization from dioxane/methanol, m.p. was 142–142.5 °C (d) with the liberation of dimethyl sulfide.

Anal. Calcd. for $C_{20}H_{30}O_5S_2$: C 57.94, H 7.29, S 15.47; found: C 58.02, H 7.36, S 15.14.

γ-Crotonolactone (Z-4-Hydroxy-2-butenoic acid, Lactone) (9)

Lactone **9** was prepared according to the procedure of Price[29] from γ-butyrolactone *via* α-bromo-γ-butyrolactone, yield 39% The proton resonance spectrum agreed with that previously published.[30] α-Bromo-γ-butyrolactone, b.p. 130–131 °C (8 mm)[31] in 88% yield from γ-butyrolactone. γ-Crotonolactone, b.p. 68–69 °C (4 mm) was prepared in 88% yield from 4-chloro-3-hydroxybutyronitrile.[32]

exo/endo-*Z-2-Carboxy-3-(hydroxymethylene)bicyclo-[2.2.2]oct-5-ene, γ-Lactone (10)*

1,3-Cyclohexadiene (5.12 g, 64 mmol) and γ-crotonolactone[33] (**10**) (5.42 g, 64 mmol) in 67.5 ml of benzene were heated at 145 °C for 24 h. The pale yellow reaction mixture was distilled. Low boiling fractions, b.p. 54 °C to 104 °C (0.6 mm), were recycled through the reaction. The fraction 105–153 °C (0.6 mm) (28.4%) was collected. Recrystallization twice from pentane/ether to gave an analytically pure sample of **10**, white needles, m.p. 89.5 °C (lit.[34] m.p. 91–92.5 °C; IR (KBr) ν_{max}/cm^{-1}: 5.71m, (CCl_4) 5.63 m (C=0); NMR (CCl_4) δ/ppm: 6.45–6.12 (m,3, 1.8 H, =CH), 4.45–4.05 (m, 1.0 H, CH_2O), 3.88–3.57 (m, 1.0 H, CH_2O), 3.22–2.88 (br s, 1.0 H, ring H2), 2.88–2.43 (m of 1 peak, 2.7 H, ring H1, H3 and H4), 1.93–0.70 (complex q, 4.1 H, ring CH2).

Anal. Calcd. for $C_{10}H_{12}O_2$: C 73.14, H 7.37; found: C 73.03, H 7.26.

Z-2-Carboxy-3-(hydroxymethylene)bicyclo[2.2.2]octane, γ-Lactone (11)

Lactone **10** (8.87 g) was reduced in ethanol using PtO_2 (51 psi), 2 h. Filtration and concentration gave a viscous brown oil which solidified and could be crystallized from pentane/ether, yield 27%, m.p. 146–147 °C. An analytical sample of 11 was obtained from pentane/ether, m.p. 147.5 °C, white needles [lit. m.p. 147 °C; IR 5.68 m (C=0)], (lit.[36] m.p. 136–138 °); IR (KBr) ν_{max}/cm^{-1}: 5.68, (CCl_4) 5.64 m (C=0); NMR (CCl_4) δ/ppm: 4.57–4.23 (m, 1.0 H, CH_2O), 4.22–3.95 (m, 1.0 H, CH_2O), 2.72–2.30 (m, 2.0 H, ring H2 and H3), 2.17–1.85 (br s, 1.0 H, ring H1), 1.85–1.22 (m of 1 peak, 9.0 H, ring CH_2 and H_4).

Anal. Calcd. for $C_{10}H_{14}O_2$: C 72.26, H 8.49; found: C 72.04, H 8.39.

E-*2-Carboxy-3-(hydroxymethylene)bicyclo[2.2.2]octane (12)*

Lactone **11** (9.24 g (55.6 mmol)) and sodium hydroxide (6.68 g) in 16 ml of water were refluxed for 32 h. The reaction mixture was then transferred with 100 ml of water to a 200 ml beaker. Acidification with hydrochloric acid (10%) led to the separation of a white solid from the aqueous solution (pH = 6). Excess diazomethane/ether was added in portions with stirring until no further reaction was apparent. Extraction with ether gave 4.19 g of a yellow oil with white crystals after concentration. Crystallization of the oil from pentane/ether gave crude methyl ester **13** (2.62 g) after a small yield of white crystals found to be the carboxylic acid **12** (0.98 g). Compound **12** was recrystallized from ethyl acetate/methanol, to give colorless needles, m.p. 162–163 °C, (**12**): IR (KBr) ν_{max}/cm^{-1}: 5.87 (s) (C=0), 2.94 (s) and 2.8–4.2 m (s, br) (O–H); NMR [$(CD_3)_2CO$] δ/ppm: 6.0–4.0 (br s, 1.9 H, OH and CO_2H), 3.78–3.32 [m including at 3.58 (d, J = 7.2 Hz), 1.9 H, CH_2O], 2.47–1.83 (m, 3.8 H, ring CH), 1.83–1.18 (m of 1 peak, 7.7 H, ring CH_2).

Anal. Calcd. for $C_{10}H_{16}O_3$: C 65.17, H 8.76; found: C 65.00, H 8.81.

The crude methyl ester was treated again with excess diazomethane until no further gas evolution took place. Excess diazomethane was destroyed with a small amount of acetic acid. Chromatography on alumina in pentane/ether gave pure (**13**): IR (neat or CCl_4) ν_{max}/cm^{-1}: 5.77 (C=0), 8.83 m (C–O–C of ether); NMR (CCl_4) δ/ppm: 3.62 (s, 3 H, CO_2CH_3), 3.25 (s, 3 h, OCH_3), 3.22 (d, 2 H, J = 7.2 Hz, CH_2O), 2.34 (br q, 1 H, ring H2), 2.07 (br s, 1 H, ring H3), 2.00–1.70 (m, 2H, ring H1 and H4), 1.70–1.00 (m of 1 peak, 8 H, ring CH_2). After recycling the yield was 90%. A final fraction from the chromatography could be deduced by NMR to be *E*-2-carbomethoxy-3-(methoxymethylene)bicyclo[2.2.2]octane: IR (neat or CCl_4) ν_{max}/cm^{-1}: 5.77 (C=0), 8.83 m (COC of ether); NMR (CCl_4) δ/ppm: 3.62 (s, 3 H, CO_2CH_3), 3.25 (s, 3 h, OCH_3), 3.22 (d, 2 H, J = 7.2 Hz, CH_2O), 2.34 (br q, 1 H, ring H2), 2.07 (br s, 1 H, ring H3), 2.00–1.70 (m, 2H, ring H1 and H4), 1.70–1.00 (m of 1 peak, 8 H, ring CH_2).

E-*2-Carbomethoxy-3-(bromomethylene)bicyclo[2,2,2]-octane* (*14*)

Bromide **14** was prepared from alcohol **12** according to Wiley. Under nitrogen 2.43 g (9.28 mmol, 1.0 equiv.) of triphenylphosphine and 7.5 ml of dimethylformamide were mixed. Alcohol **12** (1.83 g, 9.24 mmol) in 2 ml of DMF was added. Finally 0.49 ml of bromine was added. After 30 minutes the mixture was chromatogrammed on alumina and eluted with ether. The ethereal solution was washed with water, dried, and the ether removed, leaving 4.30 g of white crystals mixed with a yellow oil. The white crystals (triphenylphosphine oxide) were removed by by dilution with pentane and filtration. Removal of solvent from the filtrate gave 1.62 g of crude **14** as a yellow oil. GLPC of showed it to be contaminated with alcohol **13**. The material was rechromatographed on alumina using ether/pentane gave a yellow, somewhat thermally unstable oil. One additional chromatography gave material eluted with pentane and then ether, which was **14**. Combined fractions were distilled through a short path distillation tube, b.p. *ca.* 100 °C (0.02 mm) of **14**, 1.13 g (47%). GLPC at 200 °C, showed the bromide **14** containing a trace of alcohol **12**. NMR (CCl_4) δ/ppm: 7.88–7.15 (m, 16.1 H, ArH), 3.33 (d, 1.8 H, CH_2Br), 2.72–2.20 (br q, 1.0 H, ring H2), 2.10 (br s, 0.9 H, ring H3), 2.00–1.73 (m, 1.8 H, ring H1 and H4), 1.73–0.88 (m of 1 peak, 7.5 H, ring CH_2), methanol at 3.73 (br s, 1.0 H, OH) and 3.57 (d, 3.0 H, J = 5.5 Hz, CH_3O). An analytical sample was obtained by distillation of the chromatographed material, collection of the middle fraction, followed by short path distillation, b.p. 95 °C (0.012 mm), and then purification by preparative GLPC at 200 °C: IR (CCl_4) ν_{max}/cm^{-1}: 5.75, (neat) 5.76 m (C=0); NMR (CCl_4) δ/ppm: 3.65 (s, 2.7 H, CO_2CH_3), 3.39 (dd, 1.9 H, J = 7.7, 1.9 Hz, CH_2Br), 2.75–2.28 (br q, 1.1 H, ring H2), 2.28–2.05 (br d, 1.0 H, J = 1.9 Hz, ring H3), 2.05–1.77 (m, 2.0 H, ring H1 and H4), and 1.77–0.83 (m of 1 peak, 8.0 H, ring CH_2).

Anal. Calcd. for $C_{11}H_{17}O_2Br$: C 50.59, H 6.56; found: C 50.90, H, 6.47.

E-*2-Carbomethoxy-3-(thiomethylmethylene)bicyclo[2.2.2]octane* (*15*)

Compound **15** according to Bohme from **14** using sodium methoxide and methyl mercaptan at –60 °C in a pressure tube. The pressure vessel was opened at –78 °C, pumped free of volatiles, charged again with methyl mercaptan, and heated at 55 °C for 1 day. The cooled pressure vessel was opened and volatiles evacuated under vacuum. Ether was added. The mixture of ether solution and white salt was filtered.

The yellow ethereal filtrate was concentrated *in vacuo* leaving a pale yellow oil (4.48 g, 98%). Vacuum distillation in a short path distilling tube gave material b.p. 90–98 °C (0.02 mm) gave 4.31 g oil (94%), suitable for subsequent reaction: IR (CCl_4) ν_{max}/cm^{-1}: 5.76 (neat) 5.77 m (C=0); NMR (CCl_4) δ/ppm: 3.62 (s, 3.0 H, CO_2CH_3), 2.77–2.23 (m, 1.1 H, ring H2), 2.42 (d, 2.1 H, J = 0.6 Hz, CH_2S), 2.23–2.10 (m, 1.0 H, ring H3), 2.00 (s, 3.0 H, CH_3S), 2.00–1.77 (br s, 1.0 H, ring H1 or H4), 1.77–0.82 (m of 1 peak, 8.8 H, ring H1 or H4 and ring CH_2). Repeated distillation gave a clear colorless oil of analytically pure 15.

Anal. Calcd. for $C_{12}H_{20}O_2S$: C 63.12, H 8.83, S 14.04; found: C 63.23, H 8.91, S 13.38.

E-*2-Carbomethoxy-3-(methylenedimethylsulfonium)bicyclo[2.2.2]octane Tosylate* (**8e**)

Prepared according to a previous procedure,[3] 70% was obtained from **15** and methyl *p*-toluenesulfonate (1.2 equiv.) at 100 °C for 3 h, m.p. 114–119 °C. Recrystallization from ether/methanol and thorough drying in vacuum gave white crystals, m.p. 122–122.8 °C. IR (KBr) ν_{max}/cm^{-1}: 5.80, ($CHCl_3$) 5.81 m (C=0); NMR ($CDCl_3$) δ/ppm: 7.70 (d, 1.8 H, J = 8.1 Hz, ArH), 7.13 (d, 2.0 H, J = 8.1 Hz, CH_2S^+), 3.10 (d, 6.0 H, J = 4.5 Hz, $(CH_3)_2S^+$), 2.83–2.13 (m, 2.1 H, ring H2 and H3), 2.33 (s, 3.0 H, ArCH3), 2.13–1.93 (br s, 1.0 H, ring H1) and 1.93–0.80 (m of 1 peak, 9.1 H, ring CH_2 and H4).

An analytical sample of **8e** was obtained by one recrystallization from dioxane/methanol without heating or a nitrogen atmosphere which gave very fine white needles: m.p. 122.2–122.8 °C.

Anal. Calcd. for $C_{20}H_{30}O_5S_2$: C 57.94, H 7.29, S 15.47; found: C 57.94, H 7.30, S 14.6.

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SAŽETAK

Susjedna sulfonijeva skupina pri hidrolizi estera. III

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Pripravljeni su *Z*- i *E*-2-karbometoksi-3-(metilendimetilsulfonij)-biciklo[2.2.2]oktan *p*-toluensulfonati (**8z**, odnosno **8e**) i saponificirani pri stalnom pH kako bi se istražio utjecaj susjedne sulfonijeve skupine na brzinu reakcije. Brzine reakcije i aktivacijski parametri vrlo su bliski za oba izomera, u skladu s teorijskim predviđanjem da razdvajanje naboj-dipol i naboj-naboj kod spomenutih izomera nije znatno različito, te da je vektor karbonil-dipol gotovo okomit na pravac koji ga povezuje s atomom sumpora sulfonijeve skupine.