(10 mL), and refluxing was continued for an additional 20 min. Subsequently, the solution was cooled to room temperature and acidified with acetic acid (10 mL) and concd hydrochloric acid (10 mL) to give a suspension which was extracted with dichloromethane. Conventional further workup of the dichloromethane solution gave a dark oily residue which was subjected to column chromatography on silica gel/dichloromethane. Tolylanthracene **3** (fast-moving fluorescent fraction) was recrystallized from dichloromethane/methanol to give almost colorless crystals (yield 100 mg) which melt at 146–148 °C (lit.[27] mp 145–147 °C).

9,10-Diphenylanthracene (4) was crystallized slowly from dichloromethane solution containing about 20% methanol.

Di-9-anthrylmethane (5) and 9-(9-anthrylmethylidene)-9,10-dihydroanthracene (6) were prepared from di-9-anthrylmethanol according to the literature.[20] Dianthrylmethane was crystallized slowly from xylene solution to give yellow needle shaped crystals. Needle-shaped crystals of **6** were obtained by slow crystallization from dichloromethane/methanol.

Structure Determinations. The structures were solved by direct methods.[28] Calculations were performed with the TEXSAN crystallographic software package of Molecular Structure Corporation.[29] All pertinent crystallographic data, including atomic coordinates, are available elsewhere in printed form.[30]

Registry No. 1, 1055-23-8; 2, 23102-67-2; 3, 23674-14-8; 4, 1499-10-1; 5, 15080-14-5; 6, 55043-37-3; 9-anthrone, 90-44-8; 10-phenyl-9-anthrone, 14596-70-4; 10-*p*-tolylanthrone, 127255-73-6; 10-bromoanthrone, 1560-32-3; toluene, 108-88-3; 2·2PhMe, 138836-10-9.

(27) Lown, J. W.; Aido, A. S. K. *Can. J. Chem.* 1971, *49*, 1848.

(28) Sheldrick, G. M. *SHELXS86. Crystal Structure Solution Computer Program*, University of Göttingen, Germany, 1986.

(29) TEXSAN—TEXRAY Structure Analysis Package, Molecular Structure Corporation, 1985, The Woodlands, TX.

(30) **1a/1b**: *Z. Kristallogr., New Crystal Structures*, in press. **2**: *Ibid.*, in press. **3**: *Ibid.*, in press. **4**: *Ibid.*, in press. **5**: *Ibid.*, in press. **6**: *Ibid.*, in press.

Solvolytic Elimination Reactions of Tertiary α-$CSNMe_2$-Substituted Systems

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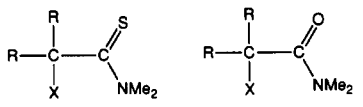
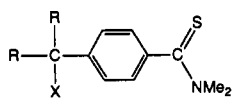
The tertiary benzylic α-$CSNMe_2$-substituted *p*-nitrobenzoates and trifluoroacetates of general structure $Ar(CH_3)C(CSNMe_2)(OCOR)$, **7** and **8**, solvolyze to give exclusively elimination products $H_2C{=}C(CSNMe_2)Ar$. A Hammett study gave a nonlinear correlation. Variation in rate with solvent ionizing power was small for the unsubstituted trifluoroacetate derivative of **8**, and the β-CD_3 isotope effect on rate was negligible. There is, however, a large isotope effect (2.5–2.8) in formation of the elimination product when $Ph(CH_2D)C(CSNMe_2)(OCOCF_3)$ solvolyzes. It is concluded that an intermediate must be involved since the product-determining step and the rate-determining step have differing isotope effects. The likely intermediate is an α-$CSNMe_2$-substituted cation (as an ion pair), despite the fact that the reaction has few characteristics of a typical E1 reaction. Tertiary norbornyl, cyclohexyl, and 2-propyl α-$CSNMe_2$-substituted systems also react to give exclusively elimination products at rates far in excess of α-$CONMe_2$ analogues. It is suggested that α-$CSNMe_2$ cations are also intermediates and that these cations undergo proton loss at an early ion pair stage. These cations are proposed to derive substantial stabilization by charge delocalization onto sulfur of the thiocarbonyl group. By way of contrast, the secondary system $CH_3CH(CSNMe_2)(OCOCF_3)$, **25**, solvolyzes to give mainly a rearranged product $CH_3CH(CONMe_2)(SCOCH_3)$ via a k_Δ mechanism involving neighboring thiocarbonyl participation leading to a cyclized ion.

Mechanisms by which the thiocarbonyl group interacts with a cationic center has been an area of interest. In this regard we have presented a preliminary study[1] on the solvolytic reactivity of systems of structure **1**. These systems react at rates that far exceed those of the carbonyl analogues **2**. We have also recently reported on the chemistry of the benzylic systems **3** under conditions where benzylic carbocations are generated.[2] In these systems,



1

2



3

the $CSNMe_2$ group has an amphielectronic effect, i.e., the cation derived from **3** can be stabilized or destabilized by the $CSNMe_2$ group depending on the nature of the R groups. We have suggested that the thioamide group can stabilize a cationic intermediate by a conjugative interaction as represented by **4b**. Theoretical studies support this suggestion.[3,4] To account for the variable electronic effect of the thioamide group on benzylic cations, we have also suggested that the importance of this effect is very dependent on the extent of positive charge development. We have also proposed that, in certain instances, the thiocarbonyl group can interact with a cationic center to form cyclized ions of type **5**. These assisted ionization rates are accompanied by large rate enhancements. In this paper we present full details on the solvolytic reactivity of a number of the thioamide containing systems.

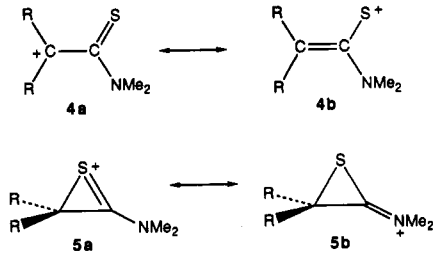
(1) Creary, X.; Aldridge, T. E. *J. Org. Chem.* 1988, *53*, 3888.

(2) Creary, X.; Aldridge, T. E. *J. Org. Chem.* 1991, *56*, 4280.

(3) Lien, M. H.; Hopkinson, A. C. *J. Am. Chem. Soc.* 1988, *110*, 3788.

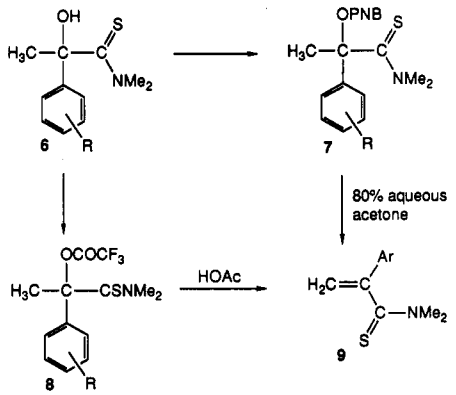
(4) For a report on the generation of **4** (R = aryl) under stable ion conditions, see: Ablenas, F. J.; George, B. E.; Maleki, M.; Jain, R.; Hopkinson, A. C.; Lee-Ruff, E. *Can. J. Chem.* 1987, *65*, 1800.

0022-3263/92/1957-1887$03.00/0



Results and Discussion

Tertiary Benzylic Systems. The *p*-nitrobenzoates **7** were prepared from the corresponding alcohols **6**. The trifluoroacetates **8** could also be prepared in ether solution, and they are stable for short periods of time as long as they remain in solution. The *p*-nitrobenzoates **7** were solvolyzed in 80% aqueous acetone where the alkenes **9** were the sole products. No trace of alcohols **6** was formed under these solvolytic conditions. Solvolyses of the trifluoroacetates **8** in acetic acid also led to the exclusive formation of alkenes **9**. Rates of *p*-nitrobenzoate solvolyses were monitored by NMR spectroscopy, while UV spectroscopy provided a convenient method for monitoring rates of the trifluoroacetates **8**. Data are shown in Table I. A limited solvent effect study on **8** (R = *p*-H) shows that rates increase somewhat as solvent polarity increases. However the response to solvent is not large. For example, the rate in trifluoroethanol is 5.9 times faster than in ethanol. By way of contrast, for the model substrates t-BuCl and 2-adamantyl tosylate, rates in trifluoroethanol are more than 10^3 times faster than in ethanol.



The results of a substituent effect study are shown in Figure 1. The Hammett plot for the *p*-nitrobenzoates is nonlinear, and the trifluoroacetates **8** also gave nonlinear behavior (not shown). For comparison purposes, literature data for cumyl *p*-nitrobenzoates[5] in the same solvent at the same temperature are shown.

As can be seen from Figure 1, rates of the thioamide derivatives **7** can dramatically exceed those of the substituted cumyl chlorides (α-CH_3 analogues) in certain cases, but this effect drops off as substituents become more electron-donating. In order to allow direct rate comparisons at convenient temperatures, the trifluoroacetates **10–12** were prepared and solvolyzed in acetic acid. The acetolysis rates of these trifluoroacetates also demonstrate the rate enhancing effect of $CSNMe_2$ relative to the $CONMe_2$ group as well as α-H and α-CH_3 analogues. Of primary interest is the reason for the nonlinear Hammett plot. Also of importance is the fact that the $CSNMe_2$ group causes rates of **7** to far exceed those of α-H (as well as α-CH_3 analogues in most cases) despite the electron-withdrawing inductive effect of this group.[2]

The nonlinear Hammett plot might suggest a mechanistic change in solvolyses of **7** as the substituents are

(5) Brown, H. C.; Ravindranathan, M.; Peters, E. N.; Rao, C. G.; Rho, M. M. *J. Am. Chem. Soc.* **1977**, *99*, 5373.

Table I. Solvolysis Rates of Substrates in Various Solvents at 25 °C

substrate	solvent	k,[a] s^{-1}
7 (R = *p*-OCH_3)	80% acetone	1.11×10^{-4}
7 (R = *p*-OCH_3)	80% EtOH	7.00×10^{-4}
7 (R = *p*-CH_3)	80% acetone	3.90×10^{-6}
7 (R = *p*-H)	80% acetone	9.43×10^{-7}
7 (R = *m*-F)	80% acetone	2.83×10^{-7}
7 (R = *m*-CF_3)	80% acetone	2.17×10^{-7}
7 (R = 3,5-$(CF_3)_2$)	80% acetone	7.23×10^{-8}
8 (R = *p*-CH_3)	HOAc	2.00×10^{-1}
8 (R = *p*-H)	HOAc	4.47×10^{-2}
8 (R = *m*-F)	HOAc	1.03×10^{-2}
8 (R = *m*-CF_3)	HOAc	8.82×10^{-3}
8 (R = 3,5-$(CF_3)_2$)	HOAc	5.29×10^{-3}
8 (R = *p*-H)	$CH_3CH_2CO_2H$	1.59×10^{-2}
8 (R = *p*-H)	CH_3OH	3.22×10^{-2}
8 (R = *p*-H)	EtOH	1.77×10^{-2}
8 (R = *p*-H)	CF_3CH_2OH	1.05×10^{-1}
10	HOAc (90.0 °C)	1.61×10^{-4}
	HOAc (70.0 °C)	1.72×10^{-5}
	HOAc (25.0 °C)	3.77×10^{-8} [b]
11	HOAc (80.0 °C)	3.02×10^{-4}
	HOAc (50.0 °C)	8.29×10^{-6}
	HOAc (25.0 °C)	2.40×10^{-7} [b]
12	HOAc	3.98×10^{-4}
13	80% EtOH	6.77×10^{-4}
14	HOAc	4.53×10^{-2}
15	HOAc	8.48×10^{-3}
16	HOAc	4.95×10^{-3}
25	HOAc (50.0 °C)	2.15×10^{-4}
	HOAc (35.0 °C)	3.21×10^{-5}
	HOAc (25.0 °C)	8.14×10^{-6}
31	HOAc (70.0 °C)	3.00×10^{-4} [b]
	HOAc (60.0 °C)	8.53×10^{-5}
	HOAC (50.0 °C)	2.27×10^{-5}
	HOAC (25.0 °C)	5.54×10^{-7} [b]
34	HOAc (80.0 °C)	2.04×10^{-4}
	HOAc (60.0 °C)	1.98×10^{-5}
	HOAc (25.0 °C)	1.57×10^{-7} [b]
41	HOAc	9.65×10^{-4}
43	HOAc	7.37×10^{-4}
47	HOAc	6.33×10^{-4}

[a] Maximum standard deviations in duplicate runs were ±1.5% for rates determined by the UV method and ±4% for rates determined by NMR. See the Experimental Section for the kinetic method. [b] Extrapolated from data at higher temperatures.

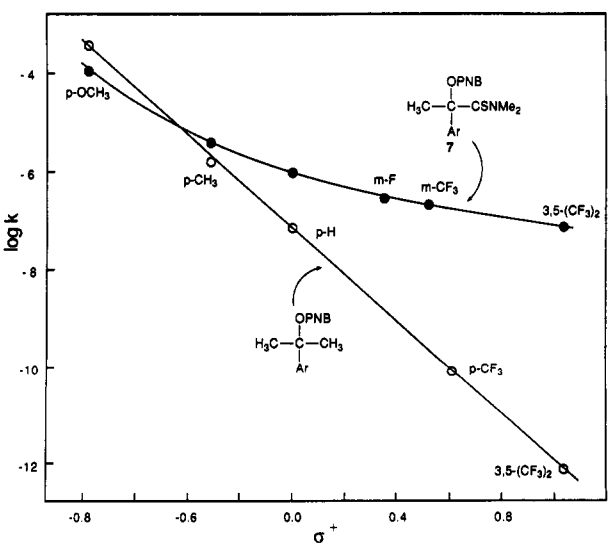
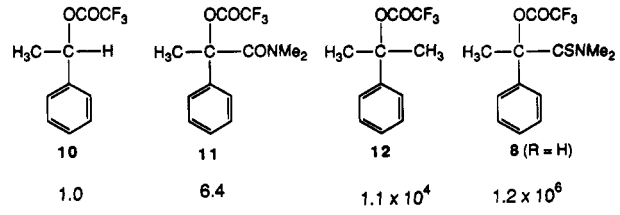


Figure 1. A plot of log k for solvolyses of *p*-nitrobenzoates in 80% aqueous acetone vs σ^+ values.

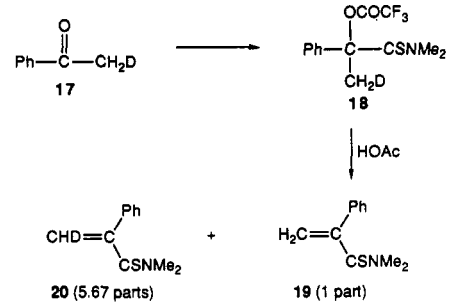


Relative Solvolysis Rates in HOAc

varied, with electron-withdrawing groups inducing a change from a k_c to a k_Δ mechanism. However, we do not believe that this simple explanation is valid for the following reasons. Firstly, the break in the Hammett plot is not a sharp break as is usually seen in k_c to k_Δ mechanistic changes.[6] Secondly, alkenes **8** are the exclusive products regardless of the aryl substituent. This product would not be expected from a k_Δ process. We will subsequently show that k_Δ processes give *no trace of elimination products* but lead instead to rearranged and unrearranged substitution products. While these arguments do not rule out a k_Δ process, they strongly suggest that a sulfur participation mechanism does not operate.

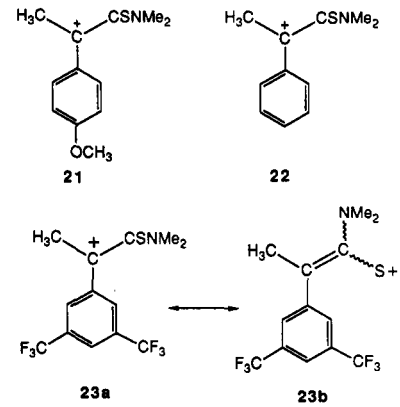
While we suspect that α-$CSNMe_2$-substituted cations are involved in the solvolyses of **7** and **8**, the possibility exists that proton loss from such a cation is rate limiting.[7] The possibility also remains that the elimination product **8** is formed in a concerted process (as in an ester pyrolysis mechanism),[8] bypassing a cationic intermediate. We have therefore probed the mechanism of reaction of **7** more deeply using β-deuterium isotope effect studies.[9] Solvolytic rate studies were carried out on the α-CD_3 analogues **13–16** and results are given in Table II. These data show that there is no primary isotope effect and therefore this elimination reaction cannot be a concerted process. Rate-limiting proton loss at an ion pair stage should also result in a large isotope effect and therefore is also improbable.

What evidence do we have for cationic intermediates in solvolyses of **7** and **8**? A nonlinear Hammett plot with an overall small response to substituents, a negligible β-deuterium isotope effect, and a relatively small solvent effect on rate do not constitute overwhelming evidence for cationic intermediates. We wanted to obtain more definitive evidence, and therefore the monodeuterated trifluoroacetate **18** was prepared. Solvolysis in acetic acid gave the elimination products **20** (both isomers) and **19** in a 5.67 to 1 ratio. In ether, where **18** also readily reacts at room temperature, the ratio of **20** to **19** was 4.91:1. In acetic acid, this corresponds to an isotope effect of 2.8 in the product-determining step, i.e., hydrogen is lost 2.8 times more readily than deuterium in the step leading to product. Keeping in mind that there is no isotope effect on the rate determining step, *the step leading to product cannot be the same as the rate-determining step*. Therefore the solvolysis mechanism must be a multistep mechanism and a reactive intermediate is necessarily involved. The likely

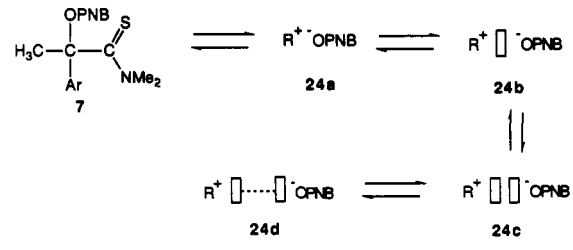


reactive intermediate is an α-$CSNMe_2$ cation.

How then do we account for the nonlinear Hammett plot? (A curved line has been drawn through the data points instead of two intersecting straight lines.) Two plausible explanations come to mind. The first involves the variable electronic characteristics of the $CSNMe_2$ group. We have presented evidence in studies on benzylic cations that the $CSNMe_2$ group is extremely variable in its cation stabilizing ability. In cases where demand for stabilization is small, then the conjugative stabilizing ability of $CSNMe_2$ is small. In cases where the demand for stabilization is large, then the $CSNMe_2$ provides much greater stabilization. Because of aryl stabilization, the demand for $CSNMe_2$ stabilization is much greater in cation **22** than in cation **21**, and the $CSNMe_2$ group responds accordingly. Forms such as **23b** have far greater importance in stabilization of **23** than analogous forms have in stabilization of **21** and **22**. It is therefore suggested that σ^+ values of the aryl substituents do not accurately reflect stabilities of the cations **21**, **22**, and **23** since the stabilizing effect of $CSNMe_2$ is so variable. Correlations of solvolysis rate of **7** with σ^+ values are not linear since the methyl group in cumyl cations does not have such variable cation-stabilizing abilities.



An alternative explanation for the nonlinear Hammett plot that should be considered is the possibility that proton loss in solvolyses of the *p*-nitrobenzoates **7** occurs from the cationic intermediate at different ion pair stages, depending on substituents. In the general ion pairing scheme shown, **24c** and **24d** represent ion pairs (beyond the solvent separated ion pair) with different levels of solvation.



Proton loss can occur in principle at any stage. However, proton loss may occur at an earlier stage when substituents

(6) For the classic example of a sharp break in a Hammett plot with the onset of a k_Δ process, see: Gassman, P. G.; Fentiman, A. F., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 2549. For a related example involving P=S participation, see: Creary, X.; Mehrsheikh-Mohammadi, M. E. *J. Org. Chem.* **1986**, *51*, 7.

(7) For an example of rate-limiting proton loss from a cation at an ion pair stage, see: Jansen, M. P.; Koshy, K. M.; Mangru, N. N.; Tidwell, T. T. *J. Am. Chem. Soc.* **1981**, *103*, 3863.

(8) (a) For pertinent reviews, see: Smith, G. G.; Kelly, F. W. *Prog. Phys. Org. Chem.* **1971**, *8*, 75. (b) Maccoll, A. *Adv. Phys. Org. Chem.* **1965**, *3*, 91.

(9) For a listing of a number of β-deuterium isotope effects in solvolytic reactions and leading references, see: Sunko, D. E.; Szele, I.; Hehre, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 5000.

Table II. β-Deuterium Isotope Effects in Solvolyses of Tertiary Benzylic Substrates

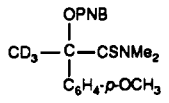
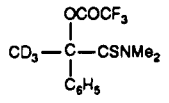
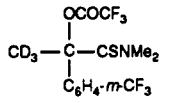
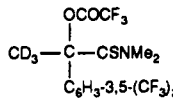
substrate	k (α-CH_3)/k(α-CD_3)
 13	1.03 ± 0.01 (80% EtOH)
 14	0.99 ± 0.02 (HOAc)
 15	1.04 ± 0.01 (HOAc)
 16	1.07 ± 0.01 (HOAc)

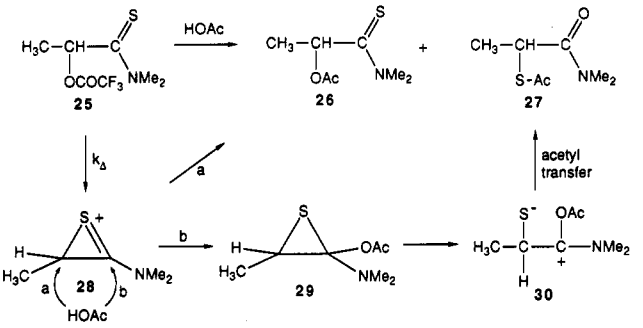
Table III. Effect of Solvent on Rates on Elimination of 41 at 25 °C

solvent	E_T	k,[a] s^{-1}
$(CF_3)_2CHOH$	69.3	4.99×10^{-3}
CF_3CH_2OH	59.3	2.49×10^{-3}
$HCONH_2$	56.6	1.33×10^{-3}
CH_3OH	55.5	6.13×10^{-4}
HOAc	51.7	9.65×10^{-4}
CH_3CN	46.0	1.63×10^{-4}
DMSO	45.0	3.88×10^{-4}
acetone	42.2	1.28×10^{-4}
$CDCl_3$	39.0	1.32×10^{-4}
tetrahydrofuran	37.4	5.99×10^{-5}
Et_2O	34.6	2.01×10^{-5}
n-Bu_2O	33.4	1.39×10^{-5}
CCl_4	32.5	1.43×10^{-5}
$CH_3CH_2CO_2H$	–	3.94×10^{-4}

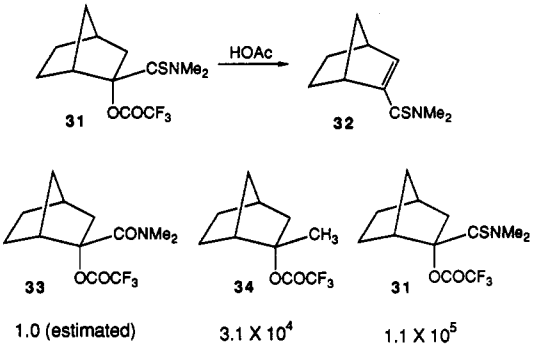
[a] Maximum standard deviations in duplicate runs were ±1.5% for rates determined by the UV method and ±4% for rates determined by NMR. See the Experimental Section for the kinetic method.

are electron-withdrawing. With electron-donating groups, the proton may be lost at a later ion pair stage. While similar effects may operate in the solvolyses of cumyl systems, it is suggested that the same spectrum of ion pairs may not be involved in solvolyses of **7**. Therefore σ^+ values do not reflect the the possibility that **7** and cumyl systems may undergo reaction with solvent at different ion pair stages. The mechanistic change which results in the nonlinear Hammett plot is therefore a subtle one involving proton loss from different ion pairs. We feel that this second potential reason for a nonlinear Hammett plot should also be considered. Some combination of the two effects could also contribute to the nonlinear Hammett plot in Figure 1.

Secondary Systems. The trifluoroacetate **25** was prepared and solvolyzed in acetic acid. In contrast to tertiary systems which give only elimination product, no trace of alkene was observed when **25** was solvolyzed. The rearranged product **27** was the major product (92%), and a minor amount (8%) of the simple substitution product **26** was also observed. Product ratios were determined by NMR from solvolysis in CD_3CO_2D since isolation procedures using an aqueous workup resulted in substantial product losses. These products are both proposed to arise via a k_Δ process which gives the ion **28** as the initial intermediate. Acetic acid capture at the tetracoordinate carbon gives the substitution product **26**, while solvent capture at the trigonal carbon gives **29**. Opening to the zwitterion **30** followed by acetyl transfer gives the major rearranged product **27**. This study establishes the properties of cyclized ions derived from thiocarbonyl participation. Such ions appear to be capable of solvent capture at each of two possible positions. Of importance is the fact that *no alkene products are observed* as in reactions proposed to involve discrete α-$CSNMe_2$ cations with β-hydrogens.



Other Tertiary Systems. In order to further probe the properties of α-thioamide-substituted cations, the norbornyl system **31** was studied. Under acetolysis conditions, the elimination product **32** was formed.[10] This system was far more reactive than the amide analogue **33**, where the mesylate derivative was necessary to achieve convenient reactivity.[11] Using a mesylate/trifluoroacetate rate ratio[12] of 10^5, the thioamide derivative **31** is estimated to be 1.1×10^5 times more reactive than the amide analogue **33**. Direct rate comparisons shows that **31** is even more reactive than the α-CH_3 analogue **34**.



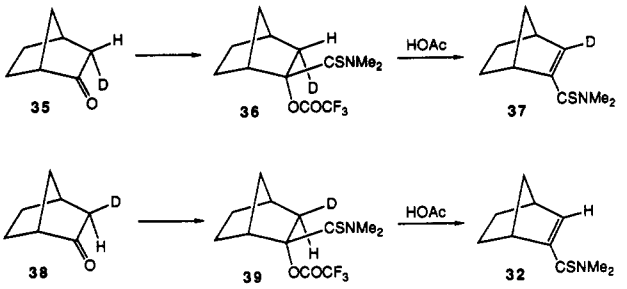
As in the case of the tertiary benzylic derivatives **7**, we have considered the possibility that the elimination product **32** was formed by a concerted ester pyrolysis type of mechanism. We therefore wanted to determine the stereochemistry of this elimination process. The stereospecifically deuterated trifluoroacetates **36** and **39** were therefore prepared from the monodeuterated ketones **35** and **38**, respectively. Acetolysis of the endo-deuterated derivative **36** gave the deuterated elimination product **37** exclusively, while the exo-deuterated derivative **39** gave completely undeuterated product **32**. This stereochemical

(10) The formation of this 1,2-elimination product contrasts with the behavior of norbornyl systems substituted with carbonyl groups, where, under solvolytic conditions, 1,3-elimination giving nortricyclane derivatives is a prominent process. See: Creary, X.; Geiger, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 4151.

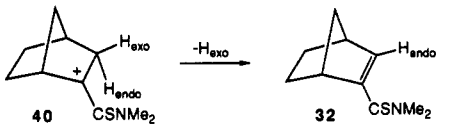
(11) Creary, X.; McDonald, S.; Eggers, M. *Tetrahedron Lett.* **1985**, *26*, 811.

(12) We have previously measured a mesylate/trifluoroacetate ratio of 2.2×10^5 in acetic acid. See: Creary, X. *J. Org. Chem.* **1979**, *44*, 3938. A value of 1.2×10^4 has also been estimated in 80% ethanol. See Noyce, D. S.; Virgilio, J. A. *J. Org. Chem.* **1972**, *37*, 2643.

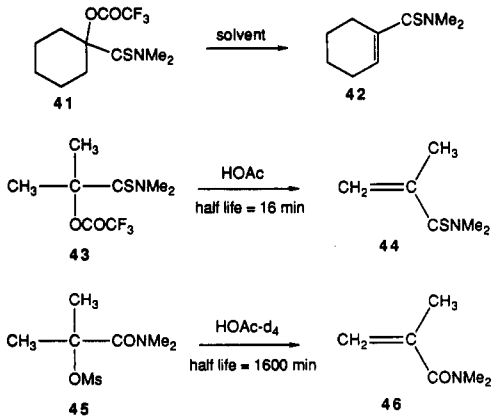
study, which shows that the exo hydrogen (or deuterium) is lost during the reaction, is inconsistent with a concerted ester pyrolysis type of mechanism. A concerted E-2 type of elimination is also unreasonable since it is also known that a significant amount (14%) of syn elimination is observed in E-2 reactions of *endo*-2-norbornyl bromide.[13]



In terms of mechanism, we favor a process involving formation of the α-$CSNMe_2$ cation **40**. This cation suffers loss of the exo hydrogen in preference to the endo hydrogen. The reason for preferential loss of the exo hydrogen is related to the fact that protonation of norbornenes occurs exclusively from the exo side (presumably for steric and electronic reasons).[14] By microscopic reversibility, the lowest energy pathway for deprotonation of cation **40** should involve loss of the exo hydrogen.



The tertiary aliphatic trifluoroacetates **41** and **43** were also prepared and solvolyzed. These substrates readily eliminate CF_3CO_2H in protic solvents such as acetic acid and trifluoroethanol giving the alkenes **42** and **44**. These substrates are remarkably reactive and undergo solvolytic elimination in acetic acid with half-lives of only 12 and 16 min, respectively, at 25 °C. The analogous amides are far less reactive, and the mesylate leaving group is required to achieve convenient reactivity. Despite the superior leaving group, the mesylate **45**, which also gives exclusively elimination product, is still 100 times less reactive than trifluoroacetate **43**.[11]



Trifluoroacetates **41** and **43** also cleanly eliminate CF_3CO_2H to give the alkenes in aprotic solvents such as $CHCl_3$, acetonitrile, and ether. Even in CCl_4, elimination of **41** occurs with a half-life of 13.5 h at 25 °C. This behavior is quite unusual in that derivatives in most solvolytic studies are generally stable in aprotic solvents such as ether and $CHCl_3$. The effect of solvent polarity on reaction rate of **41** is relatively small. The rate spread is only a factor of 350 between the most polar solvent $(CF_3)_2CHOH$ and CCl_4, the least polar solvent studied. Figure 2 shows an attempt to correlate reaction rate of **41** with the solvent polarity parameter, E_T.[15] While the correlation is not excellent, clearly there is a trend to increasing rate with increasing solvent polarity.

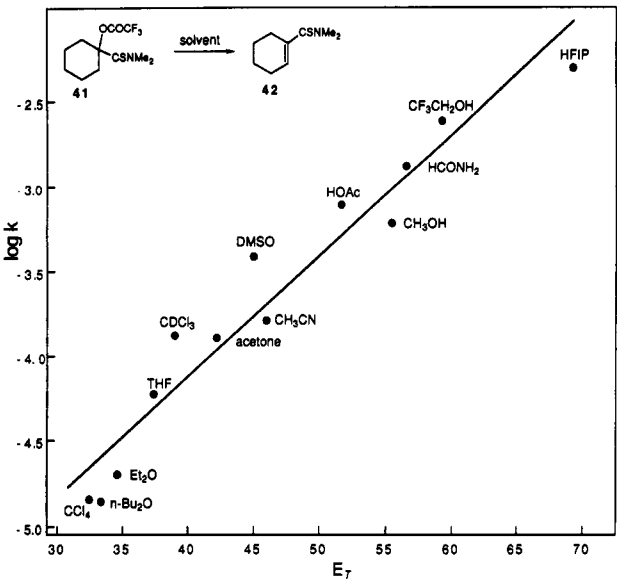
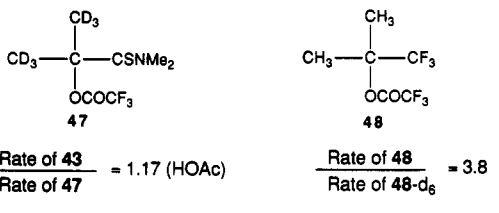
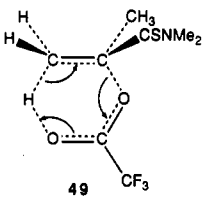


Figure 2. A plot of log k for solvolysis of **41** vs E_T values.

In order to shed further light on the mechanism of these elimination reactions of thioamides **41** and **43**, the deuterated analogue **47** was prepared in order to measure β-deuterium isotope effects. The β-d_6 isotope effect was 1.17 in acetic acid. This values is quite small and argues against the concerted elimination mechanism depicted in **49**. This isotope effect is also inconsistent with a mechanism involving rate-limiting proton loss from a reversibly formed ion pair intermediate. Such a mechanism has been observed for **48** and is characterized by a large β-deuterium isotope effect. A k_Δ process leading to a cyclized ion does





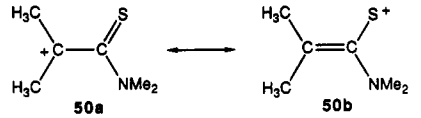
not account for the observed elimination product. A cyclized ion is expected to give rearranged products or simple substitution products (as does the cyclized ion **28**). We are left with the α-thiocarbonyl cation **50** as a likely intermediate. The low isotope effect could imply extensive charge delocalization onto sulfur as in **50b**. This would decrease the demand for hyperconjugative stabilization

(13) Stille, J. K.; Sonnenberg, F. M.; Kinstle, T. H. *J. Am. Chem. Soc.* **1966**, *88*, 4922.

(14) (a) Kropp, P. J. *J. Am. Chem. Soc.* **1973**, *95*, 4611. (b) Stille, J. K.; Hughes, R. D. *J. Org. Chem.* **1971**, *36*, 340. (c) Brown, H. C.; Liu, K.-T. *J. Am. Chem. Soc.* **1975**, *97*, 2469. (b) Brown, H. C.; Kawakami, J. H. *Ibid.* **1975**, *97*, 5521.

(15) Reichardt, C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 98.

and, in this fashion, reduce the β-deuterium isotope effect. The implication is that proton loss occurs at a very early ion pair stage, especially in aprotic solvents where anion solvation cannot be extensive.



50a 50b

Conclusions. The tertiary benzylic α-$CSNMe_2$-substituted *p*-nitrobenzoates **7** and trifluoroacetates **8** solvolyze with remarkably high reactivity relative to α-H and α-$CONMe_2$ analogues. Exclusively eliminations products are formed. Solvent effects, substituent effects, and isotope effects on rates are minimal. However, on the basis of a significant isotope effect on the product-forming step, but none on the rate-determining step, an α-$CSNMe_2$-substituted carbocation is suggested as a reactive intermediate. Other tertiary α-$CSNMe_2$-substituted systems also solvolyze to give elimination products, and α-$CSNMe_2$ cations (as ion pairs) are also proposed intermediates. Thiocarbonyl mesomeric stabilization is suggested as an important factor in stabilization of these carbocations. Proton loss from these cations occurs at a very early ion pair stage. By way of contrast, the secondary α-$CSNMe_2$-substituted system **25** solvolyzes to give mainly a rearranged product derived from a k_Δ mechanism involving thiocarbonyl participation and a cyclized intermediate.

Experimental Section

Preparation of α-Hydroxy Thioamides. General Procedure. α-Hydroxy thioamides were prepared by the previously described procedure.[4,16] A solution of lithium diisopropylamide in ether was prepared by addition of 1.2 equiv of 1.6 M *n*-butyllithium in hexanes to 1.4 equiv of diisopropylamine in ether at −78 °C. A solution of 1.0 equiv of the appropriate carbonyl compound and 1.0 equiv of *N,N*-dimethylthioformamide in a 4:1 mixture of ether–tetrahydrofuran was added dropwise to the LDA solution at −78 °C. The mixture was stirred at this temperature for 2 h and then warmed to room temperature. The mixture was quenched with water, and the organic phase was washed with more water, 10% HCl solution, and saturated NaCl solution. The organic extract was dried over $MgSO_4$ and filtered, and the solvents were removed using a rotary evaporator. The crude residue, which contained some unreacted ketone, was chromatographed on silica gel and eluted with 20% ether in hexanes. The unreacted ketone eluted with this solvent. The product α-hydroxy thioamides eluted with 35% ether in hexanes. After solvent removal by rotary evaporator, the solid products were washed with hexanes and dried under vacuum. The following reaction is representative.

Reaction of LDA prepared from 13 mL of 1.6 M *n*-BuLi and 2.44 g of diisopropylamine in 20 mL of ether with 2.078 g of acetophenone and 1.534 g of $HCSNMe_2$ in 50 mL of 4:1 ether–THF gave, after chromatography on 20 g of silica gel, 1.752 g (49% yield) of *N,N*-dimethyl-2-hydroxy-2-phenylthiopropionamide, **6** (R = *p*-H): mp 67–67.5 °C; ^1H NMR ($CDCl_3$) δ 7.42–7.24 (m, 5 H), 5.83 (br, 1 H), 3.491 (s, 3 H), 2.866 (s, 3 H), 1.854 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.16, 143.94, 128.83, 127.62, 125.36, 76.72, 47.65, 43.62, 25.99. Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 63.12; H, 7.13; N, 6.61.

6 (R = *p*-OCH_3), mp 92–93 °C, was prepared in 51% yield from *p*-methoxyacetophenone: ^1H NMR ($CDCl_3$) δ 7.29 and 6.87 (AA'BB' q, 4 H), 6.031 (s, 1 H), 3.799 (s, 3 H), 3.522 (s, 3 H), 2.922 (s, 3 H), 1.856 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.82, 159.03, 136.30, 126.80, 114.27, 76.35, 55.30, 47.81, 43.62, 25.93. Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16. Found: C, 60.10; H, 6.91.

6 (R = *p*-CH_3), mp 67–69 °C, was prepared in 51% yield from *p*-methylacetophenone: ^1H NMR ($CDCl_3$) δ 7.25 and 7.15 (AA'BB' quartet, 4 H), 5.993 (s, 1 H), 3.520 (s, 3 H), 2.910 (s, 3 H), 2.328 (s, 3 H), 1.859 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.41, 141.00, 137.33, 129.53, 125.30, 76.48, 47.69, 43.69, 25.88, 21.03. Anal. Calcd for $C_{12}H_{17}NOS$: C, 64.54; H, 7.67. Found: C, 64.67; H, 7.49.

6 (R = *m*-F), mp 46–48 °C, was prepared in 66% yield from *m*-fluoroacetophenone: ^1H NMR ($CDCl_3$) δ 7.33 (td, *J* = 8, 6 Hz, 1 H), 7.17 (dt, *J* = 8, 1.2 Hz, 1 H), 7.09 (dt, *J* = 10, 2 Hz, 1 H), 6.98 (m, 1 H), 6.02 (s, 1 H), 3.523 (s, 3 H), 2.918 (s, 3 H), 1.861 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 207.43, 163.11 (d, J_{C-F} = 245 Hz), 146.67 (d, J_{C-F} = 6.4 Hz), 130.55 (d, J_{C-F} = 8.2 Hz), 121.17 (d, J_{C-F} = 3.0 Hz), 114.73 (d, J_{C-F} = 21 Hz), 112.79 (d, J_{C-F} = 22 Hz), 76.35, 47.73, 43.63, 26.10. Anal. Calcd for $C_{11}H_{14}FNOS$: C, 58.13; H, 6.21. Found: C, 58.13; H, 6.21.

6 (R = *m*-CF_3), mp 58–60 °C, was prepared in 57% yield from *m*-(trifluoromethyl)acetophenone: ^1H NMR ($CDCl_3$) δ 7.67 (br s, 1 H), 7.56 (d, *J* = 8 Hz, 2 H), 7.48 (t, *J* = 8 Hz, 1 H), 6.024 (s, 1 H), 3.536 (s, 3 H), 2.891 (s, 3 H), 1.915 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 207.16, 145.28, 131.27 (q, J_{C-F} = 33 Hz), 129.55, 129.20, 123.97 (q, J_{C-F} = 272 Hz), 124.63 (q, J_{C-F} = 3.7 Hz), 122.22 (q, J_{C-F} = 3.5 Hz), 76.50, 47.77, 43.67, 26.29. Anal. Calcd for $C_{12}H_{14}F_3NOS$: C, 51.98; H, 5.09. Found: C, 51.66; H, 5.00.

6 (R = 3,5-bis-CF_3) (oil) was prepared in 75% yield from 3,5-bis(trifluoromethyl)acetophenone: ^1H NMR ($CDCl_3$) δ 7.85 (br s, 2 H), 7.83 (br s, 1 H), 6.039 (s, 1 H), 3.545 (s, 3 H), 2.921 (s, 3 H), 1.947 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 205.80, 147.11, 132.40 (q, J_{C-F} = 33 Hz), 125.96 (m), 123.34 (q, J_{C-F} = 273 Hz), 121.85 (heptet, J_{C-F} = 3.7 Hz), 76.47, 47.88, 43.74, 26.90; exact mass calcd for $C_{13}H_{13}F_6NOS$ 345.0622, found 345.0618.

N,N-Dimethyl-2-hydroxythiopropionamide (oil) was prepared in 26% yield from acetaldehyde: ^1H NMR ($CDCl_3$) δ 4.588 (dq, *J* = 8.5, 6.3 Hz, 1 H), 4.41 (d, *J* = 8.5 Hz, 1 H), 3.507 (s, 3 H), 3.308 (s, 3 H), 1.312 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 207.78, 67.40, 45.01, 40.59, 23.51; exact mass calcd for $C_5H_{11}NOS$ 133.0561, found 133.0560.

N,N-Dimethyl-*endo*-2-hydroxy-*exo*-bicyclo[2.2.1]heptane-2-thiocarboxamide, mp 96–97 °C, was prepared in 46% yield from norcamphor: ^1H NMR ($CDCl_3$) δ 3.486 (br s, 3 H), 3.435 (br s, 3 H), 3.20 (m, 1 H), 2.70 (br s, 1 H, OH), 2.29 (m, 1 H), 2.20 (m, 1 H), 1.94 (m, 1 H), 1.75 (m, 1 H), 1.59 (m, 1 H), 1.54–1.30 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 206.22, 84.11, 48.85, 47.15, 46.43 (br), 43.89 (br) 39.96, 36.44, 28.75, 21.91. Anal. Calcd for $C_{10}H_{17}NOS$: C, 60.26; H, 8.60. Found: C, 60.25; H, 8.60.

N,N-Dimethyl-1-hydroxycyclohexanethiocarboxamide, mp 91–92 °C, was prepared in 53% yield from cyclohexanone: ^1H NMR ($CDCl_3$) δ 4.25 (br, 1 H), 3.548 (br s, 6 H), 2.08 (m, 2 H), 1.70–1.60 (m, 7 H), 1.23 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 209.71, 77.00, 47.68 (br), 44.74 (br), 35.68, 25.03, 22.15. Anal. Calcd for $C_9H_{17}NOS$: C, 57.71; H, 9.15. Found: C, 57.52; H, 9.10.

N,N-Dimethyl-2-hydroxy-2-methylthiopropionamide (oil) was prepared in 46% yield from acetone. The LDA was prepared in THF and pure THF was used in place of an ether/THF mixture: ^1H NMR ($CDCl_3$) δ 4.80 (br, 1 H), 3.538 (br s, 3 H), 3.488 (br s, 3 H), 1.589 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 209.72, 74.03, 48.15, 44.28, 28.89; exact mass calcd for $C_6H_{13}NOS$ 147.0718, found 147.0720.

Preparation of Deuterated Acetophenones. Deuterated acetophenones of general structure $ArCOCD_3$ were prepared by base-catalyzed exchange of unlabeled acetophenones in CH_3OD–D_2O mixtures. The following procedure is representative.

Sodium metal (20 mg) was added to 6 mL of CH_3OD, and 2.20 g of acetophenone was added followed by 4 mL of D_2O. The mixture was stirred at room temperature for 2 h and then extracted twice with hexanes. The hexane extract was dried over $MgSO_4$, and the solvent was removed using a rotary evaporator. Analysis by ^1H NMR indicated >97% exchange. A second exchange was carried out using the same procedure, and the residue, after solvent removal, was distilled to give 1.78 g (79%) of $PhCOCD_3$, bp 90–91 °C (15 mm). Analysis by ^1H NMR indicated >99% exchange: ^{13}C NMR ($CDCl_3$) δ 198.20, 137.18, 133.09, 128.57, 128.29, 25.85 (heptet, J_{C-D} = 19 Hz).

p-$CH_3OC_6H_4COCD_3$, *m*-$CF_3C_6H_4COCD_3$, and 3,5-$(CF_3)_2C_6H_3COCD_3$ were also prepared by identical procedures. These were converted to the deuterated α-hydroxy thioamides using the same procedures that were used for the undeuterated acetophenones.

Preparation of *p*-Nitrobenzoates 7. *p*-Nitrobenzoates **7** (R = *p*-H) and **7** (R = *p*-OCH_3) were prepared by reaction of **6** with

(16) Bânhidai, B.; Schöllkopf, U. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 836.

n-butyllithium followed by *p*-nitrobenzoyl chloride. The other *p*-nitrobenzoates **7** (R = *p*-CH_3, *m*-F, *m*-CF_3, and 3,5-$(CF_3)_2$) were prepared by reaction of **6** with *p*-nitrobenzoyl chloride in pyridine. The following procedures are representative.

Preparation of 7 (R = H). A solution of 1.363 g of *N,N*-dimethyl-2-hydroxy-2-phenylthiopropionamide, **6** (R = *p*-H), in 40 mL of ether was cooled to −50 °C, and 5.0 mL of 1.6 M *n*-butyllithium in hexanes was added dropwise. The mixture was warmed to −10 °C, and 1.302 g of *p*-nitrobenzoyl chloride was added in a single portion. The stirred mixture was warmed to room temperature for 1 h, and then cold water and a small amount of CH_2Cl_2 were added to dissolve the precipitates. The organic extract was washed with cold dilute NaOH solution and saturated NaCl solution and dried over $MgSO_4$. The solution was filtered, and the solvents were removed using a rotary evaporator. The solid residue was collected and washed with a solution of 50% ether in hexanes to give 1.082 g (49%) of **7** (R = *p*-H): mp 122–124 °C; ^{1}H NMR ($CDCl_3$) δ 8.40–8.08 (AA′BB′ quartet, 4 H), 7.75–7.66 (m, 2 H), 7.51–7.35 (m, 3 H), 3.478 (s, 3 H), 2.974 (s, 3 H), 2.294 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 199.88, 161.84, 150.84, 141.56, 135.31, 130.88, 129.09, 128.32, 124.21, 123.89, 89.18, 46.65, 43.50, 33.46. Anal. Calcd for $C_{18}H_{18}N_2O_4S$: C, 60.32; H, 5.06. Found: C, 60.30; H, 5.17.

Preparation of 7 (R = OCH_3). In a similar fashion, a solution of 340 mg of **6** (R = *p*-OCH_3) in 15 mL of THF was reacted with 1.2 mL of 1.6 M *n*-butyllithium at −78 °C. A solution of 540 mg of *p*-nitrobenzoyl chloride in 10 mL of THF was then added. After 3 h at room temperature, a standard aqueous workup followed using cold solutions. The ether extract was washed with cold, dilute NaOH solution and dried in the usual fashion. The solvent was removed using a rotary evaporator, and the solid residue was collected and washed with a solution of 50% ether in hexanes to give 460 mg (49%) of **7** (R = *p*-OCH_3). On standing at room temperature, this *p*-nitrobenzoate decomposed to the alkene **9** (Ar = C_6H_4-*p*-OCH_3) and *p*-nitrobenzoic acid. $CDCl_3$ solutions also decompose, although dilute solutions are stable enough to obtain clean ^{1}H NMR spectra. Decomposition of more concentrated solutions appears to be autocatalytic: ^{1}H NMR ($CDCl_3$) δ 8.40–8.08 (AA′BB′ q, 4 H), 7.59 (d, *J* = 9 Hz, 2 H), 6.97 (d, *J* = 9 Hz, 2 H), 3.850 (s, 3 H), 3.474 (s, 3 H), 2.973 (s, 3 H), 2.273 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 200.18, 161.86, 159.42, 150.82, 135.37, 133.57, 130.86, 125.63, 123.86, 114.36, 89.18, 55.37, 46.67, 43.50, 33.40.

Preparation of 7 (R = CH_3). A solution of 0.99 g of the alcohol **6** (R = CH_3) in 15 mL of pyridine was stirred at room temperature, and 1.15 g of *p*-nitrobenzoyl chloride was added. After 24 h at room temperature, the reaction mixture was then transferred to a separatory funnel with Et_2O and water. Fifteen milliliters of CH_2Cl_2 was added to dissolve the solid. The organic extract was then washed with three portions of H_2O, 10% HCl, and saturated NaCl solution and dried over Na_2SO_4 and $MgSO_4$. After solvent removal using a rotary evaporator, the solid was collected and washed with 50% ether in hexanes to give 1.18 g (72%) of *p*-nitrobenzoate **7** (R = CH_3): mp 129–132 °C; ^{1}H NMR ($CDCl_3$) δ 8.40–8.27 (AA′BB′ q, 4 H), 7.56 (d, *J* = 8 Hz, 2 H), 7.25 (d, *J* = 8 Hz, 2 H), 3.469 (s, 3 H), 2.962 (s, 3 H), 2.394 (s, 3 H), 2.277 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 200.06, 161.85, 150.78, 138.58, 138.14, 135.34, 130.87, 129.71, 124.15, 123.87, 89.20, 46.64, 43.54, 33.40, 21.10. This *p*-nitrobenzoate decomposes on prolonged standing at room temperature.

Preparation of 7 (R = *m*-F). Using the above procedure, reaction of 1.03 g of alcohol **6** (R = *m*-F) in 15 mL of pyridine with 1.41 g of *p*-nitrobenzoyl chloride for 36 h at room temperature gave 0.90 g (53%) of **7** (R = *m*-F): mp 142–145 °C; ^{1}H NMR ($CDCl_3$) δ 8.37 and 8.30 (AA′BB′ q, 4 H), 7.53–7.38 (m, 3 H), 7.14–7.05 (m, 1 H), 3.471 (s, 3 H), 2.972 (s, 3 H), 2.287 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 199.17, 163.06 (d, J_{C-F} = 247 Hz), 161.68, 150.94, 144.09 (d, J_{C-F} = 7.4 Hz), 135.07, 130.87, 130.83 (d, *J* = 8.2 Hz), 123.95, 119.90 (d, J_{C-F} = 2.6 Hz), 115.36 (d, J_{C-F} = 21 Hz), 111.74 (d, J_{C-F} = 24 Hz), 46.69, 43.43, 33.42. Anal. Calcd for $C_{18}H_{17}FN_2O_4S$: C, 57.44; H, 4.55. Found: C, 57.18; H, 4.54.

Preparation of 7 (R = *m*-CF_3). Using the above procedure, reaction of 0.53 g of alcohol **6** (R = *m*-CF_3) in 15 mL of pyridine with 0.43 g of *p*-nitrobenzoyl chloride for 36 h at room temperature gave 0.64 g (79%) of **7** (R = *m*-CF_3): mp 147–150 °C; ^{1}H NMR ($CDCl_3$) δ 8.38 and 8.30 (AA′BB′ q, 4 H), 7.984 (br, 1 H), 7.894 (d, *J* = 8 Hz, 1 H), 7.671 (d, *J* = 8 Hz, 1 H), 7.592 (t, *J* = 8 Hz, 1 H), 3.478 (s, 3 H), 2.946 (s, 3 H), 2.310 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 198.83, 161.67, 150.93, 142.66, 134.91, 131.560 (q, J_{C-F} = 32 Hz), 130.84, 129.81, 127.75, 125.30 (q, J_{C-F} = 3.7 Hz), 124.01, 123.83 (q, J_{C-F} = 272 Hz), 121.08 (q, J_{C-F} = 3.7 Hz), 88.59, 46.75, 43.46, 33.58. Anal. Calcd for $C_{19}H_{17}F_3N_2O_4S$: C, 53.52; H, 4.02. Found: C, 53.27; H, 4.22.

Preparation of Trifluoroacetates 8. General Procedure. The trifluoroacetates used in this paper were prepared by reaction of the appropriate alcohol with trifluoroacetic anhydride and 2,6-lutidine in ether solvent. A solution of alcohol **6** (1.0 equiv) and 2,6-lutidine (1.6 equiv) in ether was cooled to −5 °C in an ice–salt bath, and trifluoroacetic anhydride (1.5 equivalents) was added dropwise. After 3 min at −5 °C, ice–water was added to the stirred mixture maintained at −5 °C. The water was decanted using a pipet, and cold, dilute HCl was then added to stirred mixture. The aqueous extract was again rapidly removed, and saturated NaCl solution was added. After decanting, $MgSO_4$ was added. The entire workup procedure was carried out rapidly in the reaction flask maintained in the −5 °C bath. An NMR spectrum of the ether solution showed no starting alcohol **6**. The trifluoroacetates **8** showed a benzylic CH_3 singlet at δ 2.28 and an *N*-CH_3 signal at δ 3.02. Also present is an *N*-CH_3 signal of the alkene **9** (approximately 10%) at δ 3.15–3.17. The signals at δ 2.28 and 3.02 decrease with time at room temperature while the signal at δ 3.15 increases with time. The other *N*-CH_3 signal of **8** is obscured by the large ether solvent signal. The trifluoroacetates **8** could not be isolated by solvent removal. In all cases, solvent removal led exclusively to the elimination products **9**. The solutions of **8** in ether undergo slow elimination to give **9** even at −20 °C, and they were therefore stored at −80 °C. The following procedure is representative.

Preparation of Trifluoroacetate 8 (R = *p*-H). A solution of 220 mg of alcohol **6** (R = *p*-H) and 180 mg of 2,6-lutidine in 5 mL of ether at −5 °C was reacted with 331 mg of trifluoroacetic anhydride for 3 min. After a rapid, cold, aqueous workup as described above, a portion of the ether solution was placed in an NMR tube and analyzed. The total time elapsed from addition of the trifluoroacetic anhydride until the spectrum was recorded was 14 min. NMR analysis showed no alcohol **6** and about 10% of the elimination product **9** (Ar = Ph). The trifluoroacetate **8** (R = *p*-H) showed signals at δ 2.28 and 3.02. This trifluoroacetate converted to **9** (Ar = Ph) with a half-life of 12 min in the NMR tube at 21 °C. Solutions that were used for kinetic studies were stored at −70 °C.

Solvolysis of 8 in Ether. The ether solution of trifluoroacetate **8** (R = *p*-H) prepared above was allowed to stand at 25 °C for 90 min, and the solution was then filtered to remove the $MgSO_4$ drying agent. The ether solution was washed with dilute Na_2CO_3 solution and a saturated NaCl solution and dried over $MgSO_4$. After filtration, the solvent was removed by rotary evaporator to give 198 mg (98%) of *N,N*-dimethyl-2-phenylthioacrylamide, **9** (Ar = Ph): ^{1}H NMR ($CDCl_3$) δ 7.49–7.42 (m, 2 H), 7.38–7.26 (m, 3 H), 5.619 (s, 1 H), 5.333 (s, 1 H), 3.532 (s, 3 H), 3.137 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 200.22, 150.96, 135.81, 128.78, 128.52, 125.77, 112.54, 43.18, 42.53; exact mass calcd for $C_{11}H_{13}NS$ 191.0769, found 191.0766.

Preparation of Trifluoroacetate 10. A solution of 1.280 g of α-phenylethyl alcohol and 1.800 g of 2,6-lutidine in 15 mL of ether was cooled to 0 °C, and 3.191 g of trifluoroacetic anhydride was added dropwise. After 20 min at 0 °C, a cold aqueous workup followed. The ether extract was dried over $MgSO_4$, and the solvent was removed using a rotary evaporator. Distillation gave 2.135 g (92%) of trifluoroacetate **10**: bp 75–76 °C (15 mm); ^{1}H NMR ($CDCl_3$) δ 7.37 (br s, 5 H), 6.026 (q, *J* = 6.6 Hz, 1 H), 1.663 (q, *J* = 6.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 157.40 (q, J_{C-F} = 42 Hz), 156.56, 139.20, 128.88, 126.16, 114.65 (q, J_{C-F} = 286 Hz), 77.26, 21.78; exact mass calcd for $C_{10}H_9F_3O_2$ 218.0555, found 218.0556.

Preparation of *N,N*-Dimethyl-2-hydroxy-2-phenylpropionamide (Atrolactic Acid Dimethylamide). A solution of 448 mg of 2-hydroxy-2-phenylpropionic acid (atrolactic acid) and 366 mg of *N*-hydroxysuccinamide in 8 mL of ethyl acetate was cooled to 0 °C, and 780 mg of dicyclohexylcarbodiimide in 0.5 mL of ethyl acetate was added. The mixture was stirred for 7 h at room temperature. The mixture was then filtered through Celite, and the solvent was removed by rotary evaporator. The

residue was dissolved in 8 mL of tetrahydrofuran, and excess dimethylamine (gaseous) was bubbled into the solution at room temperature. After 2 h, the solvent was again removed by rotary evaporator, and about 25 mL of ether was added. The solids were removed by filtration, and the ether solvent was removed from the filtrate by rotary evaporator. The crude residue was chromatographed on 5 g of silica gel, and the column was eluted with increasing amounts of ether in hexanes. The product eluted with approximately 50% ether in hexanes. After solvent removal, the solid was washed with pure hexanes and collected on a Buchner funnel. The yield of *N,N*-dimethyl-2-hydroxy-2-phenylpropionamide was 382 mg (66%): mp 97–99 °C; ^{1}H NMR ($CDCl_3$) δ 7.30–7.24 (m, 5 H), 3.011 (br s, 3 H), 2.624 (br s, 3 H), 1.817 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 175.06, 143.02, 128.76, 127.78, 125.40, 74.84, 38.0 (br), 37.7 (br), 24.93. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82. Found: C, 68.10; H, 7.65.

Preparation of Trifluoroacetate 11. This trifluoroacetate was prepared in 78% yield from trifluoroacetic anhydride, *N,N*-dimethyl-2-hydroxy-2-phenylpropionamide, and 2,6-lutidine in ether using the previously described procedures. The reaction mixture was allowed to warm to room temperature for 15 min before the workup. Short reaction times at 0 °C led to incomplete reaction: ^{1}H NMR ($CDCl_3$) δ 7.46–7.33 (m, 5 H), 2.980 (br s, 3 H), 2.633 (br s, 3 H), 1.955 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.62, 155.01 (q, J_{C-F} = 42 Hz), 139.33, 129.33, 129.15, 128.57, 123.56, 114.54 (q, J_{C-F} = 287 Hz), 88.42, 37.12 (br), 27.72; exact mass calcd for $C_{13}H_{14}F_3NO_3$: 289.0926, found 289.0933.

Preparation of Trifluoroacetate 12. This trifluoroacetate was prepared in 96% yield from trifluoroacetic anhydride, 2-phenyl-2-propanol, and 2,6-lutidine in ether using the previously described procedures: ^{1}H NMR ($CDCl_3$) δ 7.44–7.26 (m, 5 H), 1.888 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 155.75 (q, J_{C-F} = 42 Hz), 128.68, 128.04, 124.28, 114.46 (q, J_{C-F} = 287 Hz), 87.55, 28.05. This trifluoroacetate is stable in ether solution, and the neat compound is also stable for short periods at room temperature. However, after solvent removal, pure **12** decomposed within 30 min on standing at room temperature.

Preparation of $PhCOCH_2D$, 17. Approximately 1 mg of CF_3CO_2H was added to 10 mL of CH_3OD, and 1.030 g of 1-phenyl-1-(trimethylsiloxy)ethylene[17] was added. The solution was stirred for 36 min at room temperature. At this time, gas chromatographic analysis showed no unreacted starting material. Approximately 1 mg of Et_3N was then added, and the solvent was removed using a rotary evaporator. The residue was distilled (bp 53–54 °C, 0.7 mm) to give 0.614 g of a mixture of $PhCOCH_2D$ and $PhC(OMe)_2CH_2D$ in an 11:1 ratio as determined by NMR. The ^{1}H NMR spectrum of $PhCOCH_2D$ showed a triplet, J_{H-D} = 2.2 Hz, at δ 2.566. The ^{13}C NMR spectrum of $PhCOCH_2D$ showed a triplet, J_{C-D} = 19.5 Hz, at δ 26.32. A trace of $PhCOCH_3$ also appeared in the ^{1}H NMR spectrum at δ 2.582. The ratio of $PhCOCH_2D$ to $PhCOCH_3$ was 98:2. This mixture was used directly in the preparation of trifluoroacetate **18**.

Preparation of Trifluoroacetate 18. *N,N*-Dimethyl-3-deuterio-2-hydroxy-2-phenylthiopropionamide was prepared (55% yield) from $PhCOCH_2D$ using the same procedure that was used to prepare to unlabeled substrate **6** (R = *p*-H). The ^{1}H NMR spectrum showed a triplet, J_{H-D} = 1.8 Hz, at δ 1.856. The ^{13}C NMR spectrum showed a triplet, J_{C-D} = 19.8 Hz, at δ 25.56. About 2% of unlabeled **6** (R = *p*-H) was present in this labeled α-hydroxy thioamide. Trifluoroacetate **18** was prepared from this α-hydroxy thioamide using the same procedure that was used to prepare the undeuterated substrate **8** (R = *p*-H).

Solvolysis of 18 in Ether. An ether solution of **18** was prepared by the addition of 176 mg of trifluoroacetic anhydride to 117 mg of *N,N*-dimethyl-3-deuterio-2-hydroxy-2-phenylthiopropionamide and 89 mg of 2,6-lutidine in 3 mL of ether at −8 °C. After 4 min at this temperature, cold water was added and the previously described rapid, cold, aqueous workup was employed. The ether solution was filtered and then allowed to stand at 25 °C for 2.25 h. The ether solution was then washed with dilute Na_2CO_3 solution and dried over $MgSO_4$. The solvent was then removed using a rotary evaporator to give 101 mg (95%) of a mixture of **19** and **20**. Figure 3 shows the olefinic region of the 500-MHz ^{1}H NMR spectrum of the product mixture. The ratio of **19** to **20** was 1:4.91 as determined from the areas of the appropriate peaks.

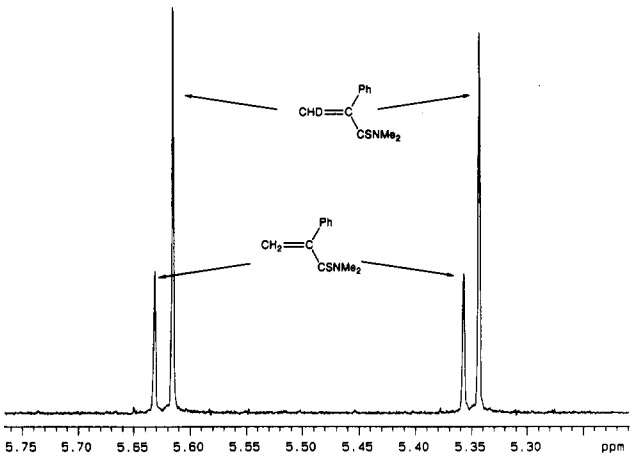


Figure 3. Olefinic region of the ^{1}H NMR spectrum of the solvolysis products of **18** in ether.

Solvolysis of 18 in Acetic Acid. An ether solution of **18** was prepared by the addition of 153 mg of trifluoroacetic anhydride to 102 mg of *N,N*-dimethyl-3-deuterio-2-hydroxy-2-phenylthiopropionamide and 78 mg of 2,6-lutidine in 2 mL of ether at −8 °C. After 4 min at this temperature, cold water was added and the previously described rapid, cold aqueous workup was employed. The cold ether solution was immediately added to 12 mL of acetic acid, and this solution was allowed to stand at room temperature for 20 min. The mixture was then taken up into ether and water. The acetic acid was carefully neutralized with solid Na_2CO_3. The ether extract was then washed with saturated NaCl solution and dried over $MgSO_4$. Solvent removal using a rotary evaporator gave 88 mg (95%) of a mixture of **19** and **20** in a 1 to 5.67 ratio as determined by 500-MHz ^{1}H NMR.

Preparation of Trifluoroacetate 25. A solution of 117 mg of *N,N*-dimethyl-2-hydroxythiopropionamide and 150 mg of 2,6-lutidine in 4 mL of ether was cooled to −5 °C, and 277 mg of trifluoroacetic anhydride was added dropwise. After 5 min, cold water was added and the ether extract was washed with dilute HCl solution, dilute Na_2CO_3 solution, and saturated NaCl solution. After being dried over $MgSO_4$ and filtered, the solvent was removed using a rotary evaporator to give 200 mg (99%) of **25** which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 5.767 (q, J = 6.6 Hz, 1 H), 3.489 (s, 3 H), 3.413 (s, 3 H), 1.634 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 198.50, 156.96 (d, J_{C-F} = 43 Hz), 114.42 (q, J_{C-F} = 286 Hz), 74.94, 45.04, 41.33, 19.07; exact mass calcd for $C_7H_{10}F_3NO_2S$ 229.0384, found 229.0382.

Solvolysis of 25 in Acetic Acid. A solution of 21 mg of **25** in 0.8 mL of CD_3CO_2D containing 14 mg of pyridine was heated at 48–50 °C for 8 h. Analysis by ^{1}H NMR showed $CH_3CH(SCOCD_3)CONMe_2$ and $CH_3CH(OCOCD_3)CSNMe_2$ in a 92:8 ratio as the only products. The reaction was also carried out in HOAc (0.1 M in NaOAc). Thus heating 158 mg of **25** in 8.5 mL of HOAc for 9 h at 48–50 °C gave, after neutralization of the HOAc with $NaHCO_3$ and standard workup, 44 mg (28%) of a mixture of **26** and **27** in an 11:89 ratio. The minor product **26** was identified by spectral comparison with an authentic sample, which was prepared by acetylation of *N,N*-dimethyl-2-hydroxythiopropionamide with acetic anhydride in pyridine with a catalytic amount of (dimethylamino)pyridine: ^{1}H NMR of **26** ($CDCl_3$) δ 5.624 (q, J = 6.6 Hz, 1 H), 3.490 (s, 3 H), 3.412 (s, 3 H), 2.130 (s, 3 H), 1.503 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.08, 170.67, 70.96, 44.92, 41.25, 21.20, 19.40; exact mass calcd for $C_7H_{13}NO_2S$ 175.0667, found 175.0663. The major product **27** was identified by spectral comparison of an authentic sample prepared as described below.

Preparation of an Authentic Sample of 27. A solution of 0.758 g of *N,N*-dimethyllactamide (prepared by reaction of ethyl lactate with excess dimethylamine at 80 °C in a sealed tube) and 0.930 g of methanesulfonyl chloride in 10 mL of methylene chloride was cooled to −50 °C, and 1.11 g of triethylamine was added dropwise. The stirred mixture was warmed to 10 °C and

(17) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.

then transferred to a separatory funnel with methylene chloride. The mixture was then washed with cold dilute HCl solution, and the CH_2Cl_2 extract was dried over $MgSO_4$. After filtration, the solvent was removed using a rotary evaporator. On standing, the mesylate derivative of *N,N*-dimethyllactamide crystallized. The solid mesylate (1.063 g, 84% yield), mp 57–59 °C, was slurried with hexanes and collected: ^1H NMR ($CDCl_3$) δ 5.470 (q, J = 6.7 Hz, 1 H), 3.133 (s, 3 H), 3.082 (s, 3 H), 2.999 (s, 3 H), 1.563 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.55, 72.89, 39.39, 36.90, 36.11, 17.92.

A solution of the sodium salt of thioacetic acid was prepared by adding 6.2 mL of 0.50 M $NaOCH_3$ in methanol to 250 mg of CH_3COSH under a nitrogen atmosphere. The mesylate prepared above (336 mg) was added in one portion to the stirred solution. After 4 h at room temperature the solvent was removed using a rotary evaporator and the residue was taken up into CH_2Cl_2 and water. The CH_2Cl_2 extract was washed with dilute Na_2CO_3 solution and dried over $MgSO_4$. The solvent was removed using a rotary evaporator, and the residue was distilled to give 191 mg (63%) of **27**: bp 70 °C (0.15 mm); ^1H NMR ($CDCl_3$) δ 4.579 (q, J = 7.0 Hz, 1 H), 3.084 (s, 3 H), 2.969 (s, 3 H), 2.350 (s, 3 H), 1.481 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 194.86, 171.14, 38.62, 37.39, 36.11, 30.19, 18.64. Anal. Calcd for $C_7H_{13}NO_2S$: C, 47.98; H, 7.48. Found: C, 47.87; H, 7.44.

Preparation of Trifluoroacetate 31. This trifluoroacetate was prepared in 96% yield from trifluoroacetic anhydride, *N,N*-dimethyl-*endo*-2-hydroxy-*exo*-bicyclo[2.2.1]heptane-2-thiocarboxamide and 2,6-lutidine in ether using the above procedure. NMR spectra were temperature dependent and became sharper at elevated temperatures: ^1H NMR ($CDCl_3$ at 45 °C) δ 3.408 (s, 3 H), 3.346 (s, 3 H), 2.321 (br, 1 H), 2.12 (d, J = 10.5 Hz, 1 H), 1.90–1.27 (m, 8 H); ^{13}C NMR ($CDCl_3$ at 45 °C) δ 199.23, 155.01 (q, J_{C-F} = 42 Hz), 114.58 (q, J_{C-F} = 287 Hz), 95.07, 47.79 (br), 46.42 (br), 46.25, 43.33 (br), 39.82 (br), 35.57, 28.34, 23.01; exact mass calcd for $C_{12}H_{16}F_3NO_2S$ 295.0854, found 295.0852.

Solvolysis of 31 in Acetic Acid. A solution of trifluoroacetate **31** (prepared from 230 mg of *N,N*-dimethyl-*endo*-2-hydroxy-*exo*-bicyclo[2.2.1]heptane-2-thiocarboxamide as described above) in 13 mL of acetic acid (0.1 M NaOAc) was heated at 63–65 °C for 16 h. The mixture was then taken up into ether and water. The acetic acid was carefully neutralized with solid Na_2CO_3. The ether extract was then washed with saturated NaCl solution and dried over $MgSO_4$. The solvent was removed using a rotary evaporator, and the residue was chromatographed on 6 g of silica gel. The product **32** eluted with 15% ether in hexanes. The yield of **32**, mp 59–60 °C, was 97 mg (46% based on *N,N*-dimethyl-*endo*-2-hydroxy-*exo*-bicyclo[2.2.1]heptane-2-thiocarboxamide): ^1H NMR of **32** ($CDCl_3$) δ 5.977 (d, J = 3.2 Hz, 1 H), 3.470 (s, 3 H), 3.365 (s, 3 H), 3.22 (m, 1 H), 3.02 (m, 1 H), 1.86–1.62 (m, 3 H), 1.47 (m, 1 H), 1.26–1.14 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 196.79, 148.59, 134.29, 48.07, 47.46, 44.10, 43.50, 42.73, 26.21, 25.94. Anal. Calcd for $C_{10}H_{15}NS$: C, 66.25; H, 8.34. Found: C, 66.33; H, 8.06.

Preparation of Trifluoroacetate 34. This trifluoroacetate, bp 44–45 °C (15 mm), was prepared in 91% yield from trifluoroacetic anhydride, *exo*-2-methyl-*endo*-bicyclo[2.2.1]heptan-2-ol, and 2,6-lutidine in ether using the above procedure: ^1H NMR ($CDCl_3$) δ 2.654 (d, J = 2.7 Hz, 1 H), 2.27 (m, 1 H), 1.80–1.18 (m with sharp singlet at d 1.569, 11 H); ^{13}C NMR ($CDCl_3$) δ 155.68 (q, J_{C-F} = 42 Hz), 114.61 (q, J_{C-F} = 287 Hz), 93.08, 46.89, 45.03, 37.62, 36.14, 27.89, 25.15, 22.41. Anal. Calcd for $C_{10}H_{13}F_3O_2$: C, 54.05; H, 5.90. Found: C, 54.26; H, 6.10.

Preparation of *endo*-3-Deuterionorcamphor (35). Sodium metal (200 mg) was dissolved in 5 mL of CH_3OD. Norcamphor (3.98 g) was added followed by 50 mL of D_2O. This mixture was refluxed for 1 h. The mixture was then cooled to room temperature and extracted with 100 mL of anhydrous ether. The ether was removed by distillation, and the procedure was repeated using a fresh 5 mL of CH_3OD (to which 200 mg of Na was added) and 50 mL of D_2O. The mixture was again extracted with anhydrous ether, and the ether was removed (without drying) by distillation. The norcamphor-d_2 (3.29 g)[18] was isolated by solid distillation at approximately 200 mm: ^{13}C NMR ($CDCl_3$) δ 218.17, 49.87, 44.58 (quintet, J = 20 Hz), 37.65, 35.16, 27.15, 24.22.

The norcamphor-d_2 prepared above was converted to 2-(trimethylsiloxy)-3-deuteriobicyclo[2.2.1]hept-2-ene using the previously described procedure (LDA; chlorotrimethylsilane) for preparation of the undeuterated material.[19] To a solution of 3.70 g of 2-(trimethylsiloxy)-3-deuteriobicyclo[2.2.1]hept-2-ene in 20 mL of tetrahydrofuran was added 0.45 g of H_2O. A few drops of CF_3CO_2H were then added (exothermic reaction), and gas chromatographic analysis showed no starting material remained. Solid Na_2CO_3 was then added followed by anhydrous Na_2SO_4. The mixture was filtered, and about 75% of the solvent was removed using a rotary evaporator. The remainder of the solvent was removed by distillation and the *endo*-3-deuterionorcamphor, **35**,[18] (2.20 g, 95%) was isolated by distillation at approximately 200 mm pressure using a solid distillation head: ^{13}C NMR ($CDCl_3$) δ 218.20, 49.87, 44.92 (t, J = 21 Hz), 37.67, 35.25, 27.16, 24.22.

Preparation of *N,N*-Dimethyl-*endo*-3-deuterio-*endo*-2-hydroxy-*exo*-bicyclo[2.2.1]heptane-2-thiocarboxamide. This substrate was prepared in 49% yield from *endo*-3-deuterionorcamphor, **35**, using the same procedure that was used to prepare the unlabeled analogue: ^{13}C NMR ($CDCl_3$) δ 206.24, 83.98, 48.81, 46.68 (t, J = 20 Hz), 46.41 (br), 43.88 (br) 39.93, 36.30, 28.68, 21.92. The 500-MHz ^1H NMR spectrum of unlabeled *N,N*-dimethyl-*endo*-2-hydroxy-*exo*-bicyclo[2.2.1]heptane-2-thiocarboxamide showed the endo C-3 hydrogen at δ 1.444 (dd, J = 13, 3.5 Hz). Examination of this region in the 500-MHz NMR spectrum of this endo-deuterated substrate showed no detectable signal. The corresponds to >99% endo-deuteration.

Preparation of *exo*-3-Deuterionorcamphor (38). A solution of 3.45 g of 2-(trimethylsiloxy)norbornene[19] in 20 mL of CH_3OD (containing 4 mg of CF_3CO_2H) was stirred at 50 °C for 3.5 h. At this time gas chromatographic analysis showed complete reaction. Et_3N (ca. 10 mg) was added, and the excess CH_3OD was removed by distillation at atmospheric pressure. The *exo*-3-deuterionorcamphor, **38**[18] (2.37 g, 81%), was isolated by distillation at approximately 200 mm of pressure using a solid distillation head: ^{13}C NMR ($CDCl_3$) δ 218.12, 49.85, 44.91 (t, J = 20 Hz), 37.68, 35.25, 27.19, 24.20.

Preparation of *N,N*-Dimethyl-*exo*-3-deuterio-*endo*-2-hydroxy-*exo*-bicyclo[2.2.1]heptane-2-thiocarboxamide. This substrate was prepared in 65% yield from *exo*-3-deuterionorcamphor, **38**, using the same procedure that was used to prepare the unlabeled analogue: ^{13}C NMR ($CDCl_3$) δ 206.24, 84.14, 48.88, 46.89 (t, J = 20 Hz), 46.44 (br), 43.86 (br) 39.98, 36.42, 28.76, 21.89. The 500-MHz ^1H NMR spectrum of unlabeled *N,N*-dimethyl-*endo*-2-hydroxy-*exo*-bicyclo[2.2.1]heptane-2-thiocarboxamide showed the exo C-3 hydrogen at δ 2.374 (m). Examination of this region in the 500-MHz NMR spectrum of the exo-deuterated substrate showed the presence of 3% undeuterated material. Mass spectral analysis also showed the presence of 3% undeuterated material.

Preparation of Trifluoroacetates 36 and 39. These labeled trifluoroacetates were prepared from the stereospecifically labeled alcohols prepared above using the same procedure used to prepare the unlabeled substrate **31**.

Solvolysis of 36 in Acetic Acid. A solution of 385 mg of **36** in 20 mL of acetic acid (0.05 M NaOAc) was heated at 70 °C for 6.5 h. The mixture was then taken up into ether, washed with water, Na_2CO_3 solution, and saturated NaCl solution, and dried over $MgSO_4$. The solvent was removed using a rotary evaporator, and the residue was chromatographed on silica gel. The product **37** eluted with 20% ether in hexanes. The ^1H NMR of **37** showed no detectable signal at δ 5.977. This corresponds to >99% deuteration. Except for the absence of the doublet at δ 5.977, the ^1H NMR spectrum of **37** was identical to that of undeuterated **32**: ^{13}C NMR of **37** ($CDCl_3$) δ 196.79, 148.53, 133.98 (t, J = 25.5 Hz), 48.09, 47.51, 44.00, 43.50, 52.75, 26.22, 25.96. Mass spectroscopic analysis of this product showed >99% deuterium incorporation.

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Solvolysis of 39 in Acetic Acid. A solution of 293 mg of **39** in 20 mL of acetic acid (0.05 M NaOAc) was heated at 70 °C for 6.5 h. After an aqueous workup as described above, the product **32** was isolated by chromatography on silica gel. ^1H and ^{13}C NMR spectra of this product were identical to those of undeuterated **32**. Mass spectroscopic analysis of this product showed <1% deuterium incorporation.

Preparation of Trifluoroacetate 41. A solution of 468 mg of *N,N*-dimethyl-1-hydroxycyclohexanethiocarboxamide and 428 mg of 2,6-lutidine in 12 mL of ether was cooled to −5 °C, and 788 mg of trifluoroacetic anhydride was added dropwise. After 5 min, cold water was added and the ether extract was washed with cold, dilute HCl solution, cold, dilute Na_2CO_3 solution, and saturated NaCl solution. The cold ether extract was dried over $MgSO_4$ and rapidly filtered. The product was kept in solution and stored at −20 °C since solvent removal and standing at room temperature led to facile elimination. The ether solvent was removed from a small portion of the solution at less than 0 °C using a rotary evaporator, and the residue was immediately dissolved in cold $CDCl_3$. NMR spectra were run at 5 °C where decomposition was not significant over the time necessary to record spectra: ^1H NMR ($CDCl_3$) δ 3.411 (s, 3 H), 3.386 (s, 3 H), 2.52–2.22 (m, 5 H), 1.80–1.40 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 200.67, 114.42 (q, J = 287 Hz), 91.58, 47.06, 43.12, 34.86, 24.46, 21.38.

Solvolysis of 41 in Acetone. The ether solvent from the above solution of **41** was removed at less than 0 °C using a rotary evaporator. The crude product **41** was immediately dissolved in 25 mL of acetone. The solution was kept at 21 °C for 40 h, and then the solvent was removed using a rotary evaporator. The residue was taken up into ether, and the solution was washed with two portions of Na_2CO_3 solution. The ether extract was then washed with saturated NaCl solution, dried over $MgSO_4$, and filtered. The solvent was removed using a rotary evaporator, leaving 404 mg (96%) of the elimination product *N,N*-dimethylcyclohex-1-enethiocarboxamide (**42**): ^1H NMR ($CDCl_3$) δ 5.616 (heptet, J = 1.9 Hz, 1 H), 3.457 (s, 3 H), 3.300 (s, 3 H), 2.283 (m, 1 H), 2.119 (m, 1 H), 1.723 (m, 1 H), 1.634 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 203.67, 141.32, 124.05, 42.96, 42.37, 27.76, 24.61, 22.33, 21.50; exact mass calcd for $C_9H_{15}NOS$ 169.0925, found 169.0924.

Preparation of Trifluoroacetate 43. A solution of 110 mg of *N,N*-dimethyl-2-hydroxy-2-methylthiopropionamide and 128 mg of 2,6-lutidine in 4 mL of ether was cooled to −5 °C, and 236 mg of trifluoroacetic anhydride was added dropwise. After 5 min, cold water was added and the ether extract was washed with cold, dilute HCl solution, cold, dilute Na_2CO_3 solution, and saturated NaCl solution. The cold ether extract was dried over $MgSO_4$ and rapidly filtered. The product was kept in solution and stored at −20 °C since solvent removal and standing at room temperature led to facile elimination. The ether solvent was removed from a portion of the solution at less than 0 °C using a rotary evaporator, and the residue was immediately dissolved in cold $CDCl_3$. NMR spectra were run at 5 °C where decomposition of **43** was not significant over the time necessary to record spectra: ^1H NMR ($CDCl_3$) δ 3.454 (s, 3 H), 3.395 (s, 3 H), 1.937 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 199.99, 114.27 (q, J = 286 Hz), 90.16, 47.06, 43.19, 28.31.

Solvolysis of 43 in Trifluoroethanol. The ether solvent from the above solution of **43** was removed at less than 0 °C using a rotary evaporator. The crude product **43** was immediately dissolved in 11 mL of trifluoroethanol. The solution was kept at 24 °C for 2.5 h, and then the solvent was removed using a rotary evaporator. The residue was taken up into ether, and the solution was washed with two portions of Na_2CO_3 solution. The ether extract was then washed with saturated NaCl solution, dried over $MgSO_4$, and filtered. The solvent was removed using a rotary evaporator leaving 225 mg (61%) of the elimination product *N,N*-dimethyl-α-methylthioacrylamide (**44**):[20] ^1H NMR ($CDCl_3$) δ 4.992 (quintet, J = 1.4 Hz, 1 H), 4.896 (quintet, J = 1.0 Hz, 1 H), 3.469 (s, 3 H), 3.321 (s, 3 H), 2.059 (t, J = 1.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.86, 147.08, 112.49, 42.90, 42.16, 22.21.

Kinetics Procedures. Rates of reaction of the substrates described in this paper were determined by either ^1H NMR, ^{19}F NMR, or UV spectroscopy. First-order rate constants were calculated by standard least-squares procedures. Maximum standard deviations in duplicate runs were ±4% for rates determined by the NMR method and ±1.5% for rates determined by UV. Solvolyses of the *p*-nitrobenzoates **7** in 80% aqueous acetone were monitored by ^1H NMR. The following procedure is representative.

About 240 mg of **7** (R = H) was dissolved in 50 mL of 80:20 v:v aqueous acetone in a volumetric flask, and the flask was placed in a constant-temperature bath at 25.0 °C. At various times 3.5-mL aliquots were quenched with ether, and the ether extracts were washed with water, 10% NaOH solution, saturated NaCl solution and dried over $MgSO_4$. The solvent was removed by rotary evaporator, and the residue was analyzed by ^1H NMR. The relative amount of remaining **7** was determined from the area of the *N*-methyl signal at δ 2.958. The relative amount of the product **9** was determined from the area of the product *N*-methyl signal at δ 3.160. Rates of the other *p*-nitrobenzoates **7** were determined by analogous procedures. The reactions was monitored over approximately 2 half-lives. First-order rate constants were calculated by standard least-squares procedures. Correlation coefficients were greater than 0.9995.

Solvolyses of the trifluoroacetates **8** in acetic acid (0.05 M in NaOAc; 1% acetic anhydride) were monitored by UV spectroscopy. In a typical procedure, 5–10 μL of a freshly prepared solution of **8** in ether was injected via syringe into 3 mL of acetic acid that had been thermally equilibrated in a constant temperature compartment of a UV spectrometer. This initiated the kinetic run. Absorbance was monitored at 283 nm. First-order rate constants were determined by standard least-square procedures. Rates of reaction of α-CD_3 analogues of **8** in acetic acid were monitored by analogous procedures. Rates of solvolyses of the *p*-nitrobenzoate **8** (R = OCH_3) and the α-CD_3 analogue in 80% aqueous ethanol were also monitored by UV spectroscopy at 255 nm. Correlation coefficients were all greater than 0.99995 except for the very reactive substrate **8** (R = CH_3) (half-life = 3.4 s) where correlation coefficients were greater than 0.9998.

Solvolyses of trifluoroacetates **10** and **11** in acetic acid were monitored by ^{19}F NMR spectroscopy. In a typical procedure, 110 mg of **11** was dissolved in 16 mL of acetic acid (0.05 M in NaOAc; 1% acetic anhydride) and 0.75-mL aliquots were sealed in glass tubes. The tubes were placed in a constant-temperature bath at the appropriate temperature, and at appropriate time intervals the tubes were withdrawn from the bath and quenched in cold water, and the contents of the tube were analyzed by ^{19}F NMR spectroscopy. The relative amount of remaining **11** was determined from the area of the corresponding ^{19}F signal. The relative amount of product was determined from the area of the corresponding ^{19}F signal due to sodium trifluoroacetate which appears 1.03 ppm upfield from the covalent trifluoroacetate **11**. Rates of **10** was monitored by analogous procedures.

The rate of solvolysis of trifluoroacetate **12** in acetic acid (0.05 M in NaOAc; 1% acetic anhydride) was monitored by UV spectroscopy at 270 nm.

The rate of solvolysis of trifluoroacetate **25** in acetic acid (0.05 M in NaOAc; 1% acetic anhydride) was monitored by UV spectroscopy at 281 nm. A solution of **25** (approximately 6×10^{-5} M) in acetic acid was prepared in a volumetric flask, and the flask was placed in a constant-temperature bath at the appropriate temperature. At appropriate time intervals 3-mL aliquots were withdrawn and absorbances were measured at 281 nm. Rate constants were calculated by standard procedures. Rate of solvolyses of trifluoroacetate **31** in acetic acid were determined by an analogous spectrophotometric procedure at 282 nm.

The rate of solvolysis of trifluoroacetate **34** in acetic acid (0.05 M in NaOAc; 1% acetic anhydride) was monitored by ^{19}F NMR spectroscopy. The product sodium trifluoroacetate signal appeared 7.9-Hz upfield from the covalent trifluoroacetate **34** signal.

Rates of solvolyses of trifluoroacetate **41** in CH_3CN, DMSO, $CH_3CH_2CO_2H$, HOAc, CH_3OH, $HCONH_2$, CF_3CH_2OH, and $(CF_3)_2CHOH$ were determined by UV spectroscopy at 290 nm. Rates in $CDCl_3$, acetone, tetrahydrofuran, diethyl ether, dibutyl ether, and CCl_4 were determined by ^{19}F NMR. The CCl_4 and $CDCl_3$ runs were carried out with approximately 2 mg of 2,6-lutidine dissolved in these solvents. In a typical procedure, solvent

(20) (a) Tamaru, Y.; Harada, T.; Iwamoto, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1978**, *100*, 5221. (b) Tamaru, Y.; Harada, T.; Yoshida, Z. *Ibid.* **1979**, *101*, 1316. (c) Tamaru, Y.; Hioki, T.; Kawamura, S.; Satomi, H.; Yoshida, Z. *Ibid.* **1984**, *106*, 3876.

was rapidly removed by rotary evaporator from a solution of about 1 mg of **33** in ether, and the appropriate solvent was immediately added. The solution was then placed in an NMR tube and sealed. The NMR tube was placed in a constant temperature bath at 25.0 °C. At periodic time intervals, the tube was analyzed by ^{19}F NMR (probe maintained at 25 °C). Depending on the solvent, the signal due to the CF_3CO_2H product appears 1.0–1.5 ppm upfield from that of the covalent trifluoroacetate.

Rates of solvolyses of trifluoroacetate **43** in HOAc and $(CF_3)_2CHOH$ were determined by UV spectroscopy at 290 nm.

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds **8** (R = 3,5-bis-CF_3), $CH_3CH(OH)CSNMe_2$, $(CH_3)_2C(OH)CSNMe_2$, **9** (Ar = Ph), **10**, **11**, **25**, **26**, **31**, and **42** (20 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

The Strain Energy of Cyclotetradecane Is Small

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Contrary to earlier reports, we show the strain energy of cyclotetradecane is both small and similar to that of other moderately sized cycloalkanes. Our finding is derived by use of semiempirical rules, MM3 molecular mechanical calculations, chemical intuition, and new measurements of heats of sublimation (mean temperature = 39 °C, 23.4 kcal mol^{-1}; corrected to STP, 23.5 kcal mol^{-1}) and vaporization (mean temperature = 70 °C, 14.9; corrected to STP, 15.6 kcal mol^{-1}).

We wish to report that, contrary to results from earlier studies,[1,2] cyclotetradecane is nearly strainless. Cycloalkanes are conceptually among the simplest classes of organic compounds because they are composed of only carbon and hydrogen and of only one type of structural component. As such, they are important archetypes for our understanding of the interrelations of structure and energy for heterocyclic, substituted, and polycyclic systems. The results are applicable to crown ethers, cryptands, carcerands, and even more elegant complexing species,[3] as well as to highly functionalized derivatives such as the calicheamycins and esperamycins, and the other new enediyne antitumor agents.[4]

Regardless of the precise definition of strain energy and choice of the input parameters,[5] the values for cycloalkanes are not a monotonic function of ring size. Table I gives the values of these strain energies using the assumption that cyclohexane is strainless.[6] We find 3- and 4-membered rings are highly, and nearly identically, strained; 5- and 7-straddle cyclohexane are only moderately strained; 8–11-membered rings are all rather strained; and 12-membered and beyond generally have little strain.

Despite the diverse intricacies influencing the values for moderately sized rings, the value of the $n = 14$ species still seems badly out of line. We questioned whether the cyclotetradecane value is correct. One reason for our skepticism is that strain energy refers to gas-phase species at 25 °C and 1 atm, while most experimental measurements of heat of combustion (and thus the derived heat of formation) refer to condensed phases. About a decade ago, an empirical relation for predicting heats of vaporization

Table I. Strain Energies (in kcal mol^{-1}) of the Cycloalkanes as a Function of Ring Size *n* and the Following Definition of Strain Energy

$$SE(g, (CH_2)_n) \equiv \Delta H_f[g, (CH_2)_n] - 7_6\Delta H_f(g, (CH_2)_6)$$

n	SE	*n*	SE	*n*	SE
3	27.5	8	9.6	13	5.0
4	26.4	9	12.5	14	11.6
5	6.3	10	12.3	15	1.7
6	0	11	11.2	16	1.9
7	6.2	12	4.0	17	-3.5

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(1) The original thermochemical data on cyclotetradecane is found in: Frisch, M. A.; Bautista, R. G.; Margrave, J. L.; Parsons, C. G.; Wotiz, J. H. *J. Am. Chem. Soc.* **1964**, *86*, 335. For completeness, we note an earlier study that results in a heat of formation of solid cyclotetradecane of −89.5 ± 0.3 kcal mol^{-1} (Coops, J.; Van Kamp, H.; Lambregts, W. A.; Visser, B. J.; Dekker, H. *Rec. Trav. Chim.* **1960**, *79*, 1226).

(2) For a review of the strain energy of cycloalkanes and of other building blocks of strained molecules, see: Greenberg, A.; Liebman, J. F. *Strained Organic Molecules*; Academic Press: New York, 1978; Chapter 3 and numerous references cited therein. For a review of the thermodynamic properties of hydrocarbons, see: Domalski, E. S.; Hearing, E. D. *J. Phys. Chem. Ref. Data* **1988**, *17*, 1637.

(3) See, for example, the Nobel Prize lectures of: Cram, D. J.; Lehn, J. M.; Pedersen, C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1009, 90, and 1021, respectively.

(4) Lee, M. D.; Ellestad, G. A.; Borders, D. R. *Acc. Chem. Res.* **1991**, *24*, 235.

(5) Van Vechten, D.; Liebman, J. F. *Isr. J. Chem.* **1981**, *21*, 105.

(6) Since the standard heat of formation of gaseous cyclohexane is −29.5 (±0.2) kcal mol^{-1}, the heat of formation of the strainless CH_2 increment is taken to be −4.92 kcal mol^{-1}. (All otherwise unreferenced thermochemical information in this paper is taken from the archival and often "averaged" source: Pedley, J. B.; Naylor, R. D.; Kirby, S. P. *Thermochemical Data of Organic Compounds*, 2nd ed.; Chapman & Hall: London, 1986. Had we used the results of Frisch et al., op. cit. for the heat of formation of solid cyclotetradecane instead, we would have concluded that this species was strained by 12.1 kcal mol^{-1}.)

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