Kinetic Deuterium Isotope and Electronic Effects in the Silver(I) Promoted Type γ Isomerization of 1-Alkyltricyclo[4.1.0.0^{2,7}]heptanes. Mechanistic Analysis of the Formation of Bicyclo[3.2.0]hept-6-enes[1]

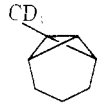
Leo A. Paquette* and Gerald Zon[2]

Contribution from the Department of Chemistry, The Ohio State University, Columbus, Ohio 43210. *Received July 26, 1973*

Abstract: The Ag(I)-catalyzed isomerization of 1-carbomethoxytricyclo[4.1.0.0^{2,7}]heptane follows second-order kinetics and proceeds (slowly) to give mainly 2-carbomethoxy-1,3-cycloheptadiene. The marked changeover in product distribution relative to related compounds with alkyl groups at C_1 is attributed to an electronic effect which operates however to decelerate chiefly the type γ rearrangement pathway. Deuterium isotope effects have been determined for *syn*-3-methoxy-1-methyltricyclo[4.1.0.0^{2,7}]heptane carrying isotopic label at C_2 and at C_7. In the latter instance, the formation of 6- and 7-methylbicycloheptenes is affected identically (k_H/k_D = 1.45). Deuterium substitution at C_2, in contrast, partitions the interaction mechanisms so as to enhance the production of the 6-methyl isomer (k_H/k_D = 0.87) and retard formation of the 7-methyl derivative (k_H/k_D = 1.17). These observations have been incorporated with previous results to provide detailed mechanistic interpretations of the generalized type α and γ rearrangements.

Placement of an alkyl group at C_1 of the tricyclo[4.1.0.0^{2,7}]heptane ring system diverts the behavior of the parent hydrocarbon when exposed to Ag^+ salts away from exclusive type α rearrangement[3,4] to as many as three other reaction channels (termed the β, γ, and δ processes[4]). An increase in the effective steric bulk of the 1-substituent eventuates in an additional decreased tendency for conversion to 1,3-cycloheptadiene product (type α isomerization) accompanied by a simultaneous enhancement in bicyclo[3.2.0]hept-6-ene formation (the type γ pathway).[4] This relationship between diminished accessibility of Ag^+ to the C_1 region and kinetically controlled product distribution is reflected in the individual α:β:γ:δ profiles:[5] 1-methyl, 26.4:29.3:44.3:0;[3b,c] 1-(2-methoxyethyl), 19:27:54:0;[4] 1-isopropyl, 8:13:66:0;[4] 1-*tert*-butyl, 3:2:92:2.[4]

A kinetic comparison of **1** (26.5:25.8:45.6:0) and **2**



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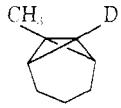
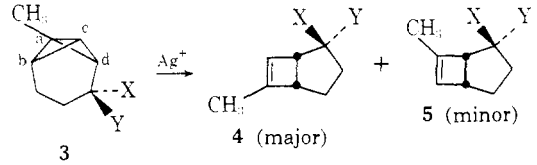


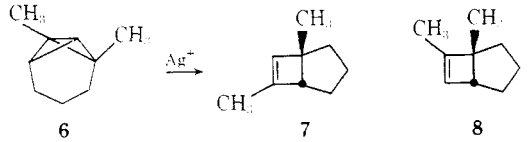
2

(35.3:34.9:29.8:0) with their nonlabeled counterpart provides further insight into the nature of these reorganizations.[6] With particular regard to the type γ rearrangement, the small deuterium isotope effect (k_H/k_D = 1.03) shown by **1** has been taken to mean that the carbon atom bearing the methyl group (C_1) does not attain a degree of carbonium ion character in the rate-determining step which permits substantial hyperconjugative release from the substituent. Present interpretation of the quite large fractionation factor (k_H/k_D = 1.74) exhibited by **2** for the same conversion is that the C_7–H bond is extensively affected[6b] but not migrated to a proximate carbon atom.[1] To elucidate the precise bond (or bonds) ruptured initially during the type γ rearrangement, tricyclo[4.1.0.0^{2,7}]heptanes with increasingly sophisticated substituent arrangements were synthesized and treated with catalytic quantities of silver perchlorate in benzene.[1,7] The isomerizations were shown to be not only completely stereospecific, but regioselective as well, implicating approach of Ag^+ toward C_7 with ensuing *formal* competitive rupture of the b–c (more kinetically favored) and c–d edge bonds (*cf.* **3**).



3 4 (major) 5 (minor)

Despite these advances, a detailed mechanistic analysis of the type γ isomerization was still lacking.[6,8] As an example of an additional factor requiring consideration, we cite the behavior of **6** (12:28:52:8) which gives rise to **7** (and not **8**) as the sole type γ product.[3c,6b] We



6 7 8

have now probed further the role played by the electronic nature of the 1-substituent in this rearrangement

(1) Silver(I) Ion Catalyzed Rearrangements of Strained σ Bonds. XXII. The previous paper is G. Zon and L. A. Paquette, *J. Amer. Chem. Soc.*, **96**, 215 (1974).

(2) National Institutes of Health Postdoctoral Fellow, 1972–1973.

(3) (a) L. A. Paquette, G. R. Allen, Jr., and R. P. Henzel, *J. Amer. Chem. Soc.*, **92**, 7002 (1970); (b) L. A. Paquette, R. P. Henzel, and S. E. Wilson, *ibid.*, **93**, 2335 (1971); (c) L. A. Paquette, S. E. Wilson, R. P. Henzel, and G. R. Allen, Jr., *ibid.*, **94**, 7761 (1972).

(4) This useful abbreviated notation system for describing the various bond reorganizations of the tricyclo[4.1.0.0^{2,7}]heptanes is discussed by L. A. Paquette and G. Zon, *ibid.*, **96**, 203 (1974).

(5) These profiles serve as a convenient shorthand notation system for the rapid summation of the relative product distribution displayed by a given molecule. Familiarity with these profiles provides an exceptionally concise way in which to store and retrieve large amounts of data (see Table II for example).

(6) (a) L. A. Paquette and S. E. Wilson, *J. Amer. Chem. Soc.*, **93**, 5934 (1971); (b) L. A. Paquette, S. E. Wilson, and R. P. Henzel, *ibid.*, **94**, 7771 (1972).

(7) G. Zon and L. A. Paquette, *J. Amer. Chem. Soc.*, **95**, 4456 (1973).

(8) P. G. Gassman and T. J. Atkins, *J. Amer. Chem. Soc.*, **93**, 4597 (1971).

and have amalgamated the stereospecific and regioselective behavior of 1,3-disubstituted trichloheptanes with a detailed kinetic deuterium isotope effect study. The present results permit a more elaborate assessment of the title rearrangement than previously possible.

Results

Synthesis and Rearrangement of 1-Carbomethoxytricyclo[4.1.0.0^{2,7}]heptane. Because all 1-substituted tricycloheptanes examined to date possess bridgehead substituents capable of favorable interaction with developing electron-deficient centers, the effect of these groups on the four types of rearrangement will be identical in direction although not necessarily comparable in magnitude. We considered that perturbation of the electronic makeup of the C_1 substituent from electropositive to electronegative would provide needed information concerning its effective control of mechanistic partitioning in these systems.

For the synthesis of 1-carbomethoxytricycloheptane **10**, the lithium salt of **9** was prepared by treatment with *n*-butyllithium–tetramethylethylenediamine (TMEDA) and subsequently introduced by inverse addition to excess methyl chloroformate. When treated with $AgClO_4$ in anhydrous benzene, ester **10** expectedly[9] exhibited a much slower rate of rearrangement relative to those previously determined for several 1-alkyl derivatives (Table I). However, the product mixture

Table I. Isomerization Rate Data for 1-Substituted Tricyclo[4.1.0.0^{2,7}]heptanes ($AgClO_4$, C_6H_6, 40°)

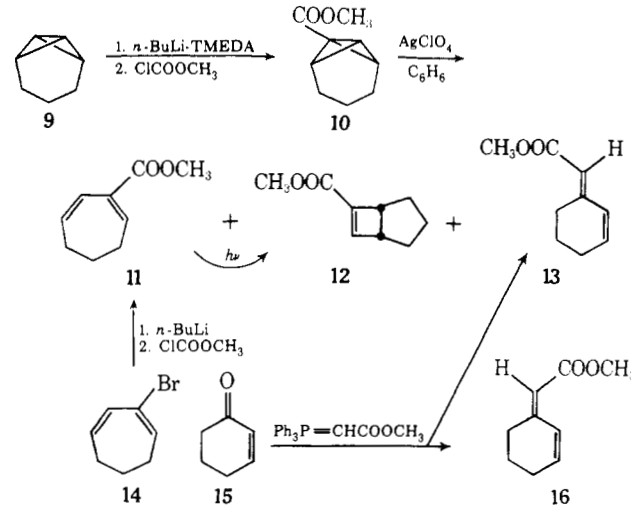
R	$k_{overall}$, M^{-1} sec^{-1}	Rel rate	Ref
CH_2OCH_3	6.71×10^{-3}	1785	4
CH_3	5.70×10^{-3}	1520	3c
$CH_2CH_2OCH_3$	3.35×10^{-3}	895	4
H	2.27×10^{-3}	605	3c
$CH(CH_3)_2$	2.14×10^{-3}	570	4
$C(CH_3)_3$	1.31×10^{-4}	35	4
$COOCH_3$	3.75×10^{-6}	1	Present work

now consisted almost entirely (96.6%) of 2-carbomethoxy-1,3-cycloheptadiene (**11**, Chart I). This major product was identified by direct comparison with an authentic sample synthesized independently from bromide **14**. Two of the three minor products were shown to be bicycloheptene **12** (0.4%) and ethylidenecyclohexene **13** (1.9%), but the remaining component (1.1%) has not yielded to characterization. The gross structure of **12** was consistent with the spectral evidence and formation upon photoisomerization of **11**. Diene ether **13** was readily available as the less dominant isomer (30%) from Wittig reaction of 2-cyclohexenone with carbomethoxymethylenetriphenylphosphorane.

The product distribution did not change within experimental error as reaction proceeded and control experiments showed that **11**, **12**, and **13** were stable to the reaction and work-up conditions. Accordingly, the absence of significant quantities of bicycloheptene **12** (type γ product) denotes that the carbomethoxy substituent deters operation of that pathway which is

(9) The kinetic behavior of carbomethoxy substituted cubyl systems serves as a reliable analogy: (a) L. A. Paquette and J. S. Ward, *Tetrahedron Lett.*, 4909 (1972); (b) L. Cassar, P. E. Eaton, and J. Halpern, *J. Amer. Chem. Soc.*, **92**, 6366 (1970).

Chart I. Synthesis and Ag^+-Catalyzed Rearrangement of 1-Carbomethoxytricyclo[4.1.0.0^{2,7}]heptane



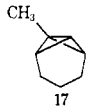
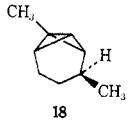
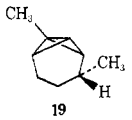
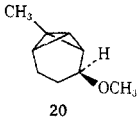
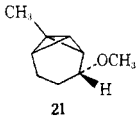
preferred in the case of electron-releasing groups. This effect is not steric in origin since the larger *tert*-butyl function in fact enhances partitioning in the γ direction (3:2:92:2); the role of prior Ag^+ complexation to the carbonyl group, if extant, remains unknown. Seemingly, the consequence of carbomethoxy substitution is electronic in origin and such that the major driving force behind type γ isomerization is now destabilized as a result of this interaction. This observation suggests that the relative degree of positive charge buildup at C_1 required of the type γ rearrangement is significantly greater than that (if any) for the type α rearrangement. Both processes are recognized to involve initial electrophilic attack by Ag^+ at C_7,[4,6b] the mechanistic feature presumably distinguishing them being the level of cationic character which can be tolerated at C_1. However, some restriction must be placed on the maximum level of electronic depletion which actually operates at C_1 since it is recognized on the basis of studies with **1** that the alkyl side chain does not find it possible to exert maximum hyperconjugative release.[6]

Kinetic and Deuterium Isotope Effect Studies. The rates of isomerization of **21** and several congeners (Table II) were found to obey the rate law represented by eq 1. Factorization of $k_{overall}$ into the individual

$$\ln\left(\frac{[\text{tricycloheptane}]_t + [\alpha]_t + [\beta]_t + [\gamma]_t}{[\text{tricycloheptane}]_t}\right) = k_{overall}[AgClO_4]t \quad (1)$$

catalytic rate constants was accomplished as before.[4] Although such kinetic comparisons based upon *product formation* serve the very useful purpose of permitting direct assessment of the various rearrangement pathways in closely related molecules such as **17**–**21**, the method is not without an inherent assumption. The difficulty is not present in one-step isomerizations where the kinetically significant features are directly relatable to product composition. However, in reactions where intermediates are involved, the relative amounts of products depend upon how these intermediates react, and not necessarily on how the starting material reacts. Insofar as the Ag^+-catalyzed rearrangements under consideration are concerned, we have reason to believe that the α, β, and γ bond reorganiza-

Table II. Isomerization Rate Data for 1,3-Disubstituted Tricyclo[4.1.0.0^{2,7}]heptanes ($AgClO_4$, C_2H_6, 40.0°)

Compound	Profile[a]	$k_{overall}$, M^{-1} sec^{-1} [b,c]	Rel rate
 17	26:29:44:0	5.10×10^{-3}	22
 18	13:14:73:0	3.31×10^{-3}	14
 19	28:8:64:0	7.25×10^{-3}	32
 20	2:27:71:0	2.30×10^{-4}	1
 21	4:5:91:0	5.12×10^{-4}	2.2

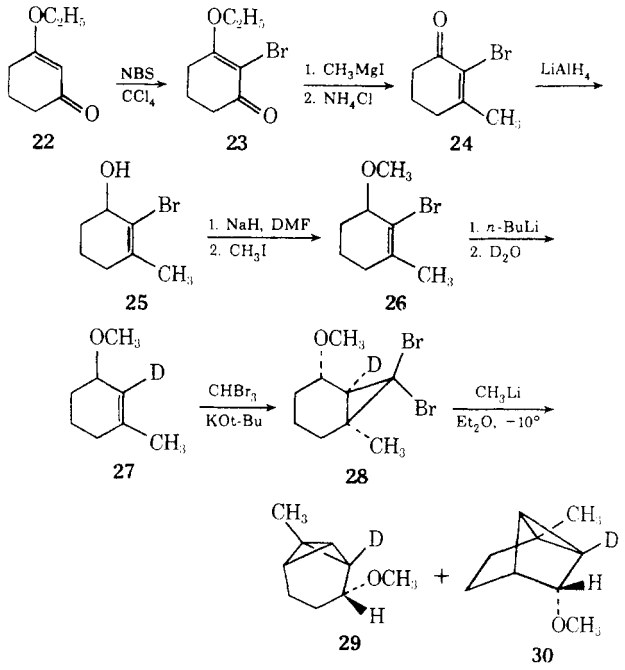
[a] Relates to the distribution of products according to the α, β, γ, and δ pathways, respectively. [b] Catalytic rate constants for disappearance of starting material measured over 75–90% reaction except in the case of **20** (15–25% conversion) and **21** (5–8% conversion). [c] The calculation of individual rate constants (k_i) may be readily accomplished, if desired, through multiplication of $k_{overall}$ by a component (or subcomponent where more than one isomer arises along a particular reaction channel) of the profile.

tions take place by way of intermediates which are unique to each process. As a consequence of the *apparent* lack of crossover of these intermediates, the possibility of relating product distribution directly to initial partitioning of the starting tricycloheptane among the three intermediates is indicated to be meaningful but as yet incompletely confirmed by experiment.

The overall rates of disappearance of **19**, **17**, **18**, **21**, and **20** (Table II) exhibit a relative reactivity order of 32:22:14:2.2:1.0, respectively. The fact that both 3-methoxy substituted derivatives are the slowest to rearrange denotes that the presence of an ether oxygen at this site exerts a small rate-retarding effect on the total process, perhaps as a result of reversible coordination with the Ag^+ catalyst. A further interesting aspect of these kinetic studies is that somewhat faster rates are encountered when the C_3 substituent is stereoproximal to the bridgehead methyl group, at least relative to its stereodistal diastereomer (compare **19**/**18** and **21**/**20**). Very probably as the result of coincidence, the kinetic inequity is 2.2–2.3 in the two series.

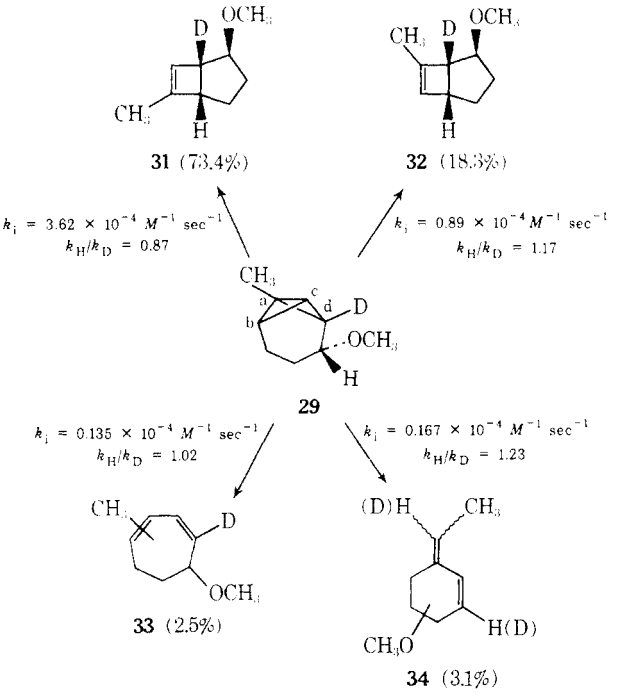
Attention was next directed to structural modification by deuterium substitution. For practical reasons, the decision was made to utilize the readily accessible proximally substituted 3-methoxy-1-methyltricycloheptane nucleus (**21**). A comprehensive isotope effect study required substrates which ideally incorporated deuterium at C_2 and at C_7. Synthesis of the "wing" labeled derivative **29** was achieved in moderate yield according to Chart II.

Chart II. Preparation of "Wing" Deuterium Labeled Tricyclo[4.1.0.0^{2,7}]heptane **29**

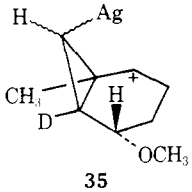


Kinetic analysis of the Ag^+-catalyzed rearrangement of **29** was carried out under conditions identical with those employed for **21**. In actual fact, the isomerizations of **21**, **29**, and also **39** (see below) were conducted simultaneously to remove small discrepancies which could arise in time-lag experiments. Under these matched conditions, **29** rearranged with a $k_{overall} = 5.33\ (\pm 0.12) \times 10^{-4}\ M^{-1}$ sec^{-1} corresponding to a total fractionation factor (k_H/k_D) of 0.96 (± 0.02). In Chart III are listed the product distribution, individual

Chart III. Product Distribution, Catalytic Rate Constants, and Kinetic Deuterium Isotope Effects Arising from Rearrangement of **29** (0.0924 *M* $AgClO_4$, C_6H_6, 40.0 ± 0.1°)



catalytic rate constants (k_i), and kinetic isotope effect values for the various processes. Our results show that the substitution of deuterium for hydrogen at position 2 exerts nil effect on the rate-determining transition state of the type α rearrangement which gives 1,3-cycloheptadiene **33**. This observation suggests that small structural changes have taken place at the isotopically substituted position probably as the direct result of kinetically preferred b–c bond cleavage to give intermediate **35**. This directional specificity places the developing positive charge as remote as possible from the electronegative oxygen center. In contrast, isomerization to **34** (type β rearrangement) is accompanied by a significant fractionation factor which is anticipated under conditions where argento carbonium ion formation (*cf.* **36**) is rate controlling. The



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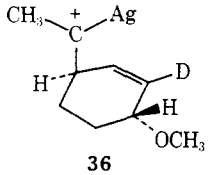

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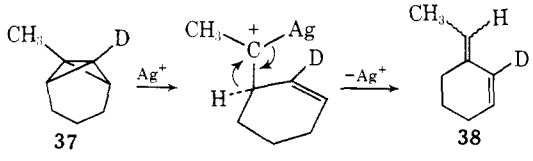
observed isotope effect is consistent with some C–D bond twisting required to generate the double bond and a decrease in the zero point energy (ZPE) of the C–D bond bending motion. The latter may arise from hybridization alterations in the C_2 carbon atom but more likely occurs as a result of partial positive charge development at this center in the transition state leading to **36**.[6] This conclusion derives some support from the behavior of **37** during its conversion to ethylidenecyclohexene **38**.[6] In this example, the isotope effect



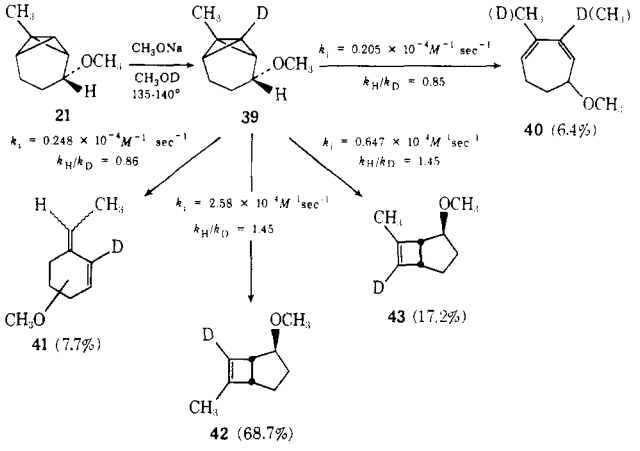
37 **38**

is inverse (k_H/k_D = 0.95) chiefly as a consequence of the very large hybridization change ($sp^{1.46}$ C–D → sp^2 C–D)[6,10,11] which occurs at C_7 to increase the ZPE of the C–D bending and stretching modes.

Most intriguing is the type γ rearrangement of **29** where the rate-determining steps are seen to be markedly influenced, but in *oppisite* directions. Deuterium substitution at C_2 has a positive kinetic influence on the production of 6-methylbicycloheptene **31** (k_H/k_D = 0.87) but an adverse decelerative effect on the formation of the less dominant 7-methyl isomer **32** (k_H/k_D = 1.17). Because the type γ partitioning of **29** between **31** and **32** is inextricably related to initial competitive formal rupture of bonds b–c or c–d,[1] the deuterium isotope effects distinguish the mutual interrelationships involved in these chemical changes (see Discussion).

Attempted synthesis of **39** by standard lithiation methods[3c,11] led to the consumption of **21** without formation of isolable products. We reasoned that the lifetime of the apparently unstable tricycloheptyl anion had to be minimized and the successful realization of deuterium exchange was indeed achieved under such conditions. When **21** was exposed to a solution of sodium methoxide in CH_3OD and heated in a sealed tube at 135–140° for 66 hr,[12] isotopically pure (>96% d_1) **39** was isolated in 41% yield after vpc purification. Under conditions of rearrangement identical with those employed above, **39** was found to exhibit a marked sensitivity to C_7 deuterium substitution (Chart IV).

Chart IV. Synthesis and Ag^+-Catalyzed Rearrangement Data for **39** (0.0924 *M* $AgClO_4$, C_6H_6, 40.0 ± 0.1°)



The catalytic rate constant for total rearrangement of **39** ($k_{overall}$) was depressed relative to that of **21**. Because the product composition lies heavily in favor of bicycloheptenes **42** and **43**, the overall rate retardation exhibited by **39** (k_H/k_D = 1.36 ± 0.06) will be concentrated primarily in these products. In contrast to the behavior of **29**, however, the interaction mechanism responsible for partitioning to 6- and 7-methylbicycloheptenes was *identically* affected (k_H/k_D = 1.45) in the decelerative sense. These pronounced deuterium-promoted kinetic decreases do not come into play in the subsidiary isomerizations of **39** along the type α (**40**, k_H/k_D = 0.85) and β (**41**, k_H/k_D = 0.86) reaction manifolds. These latter values compare closely to those observed in our earlier study of **37**[6] and connote that the same mechanisms are operative here.

Discussion

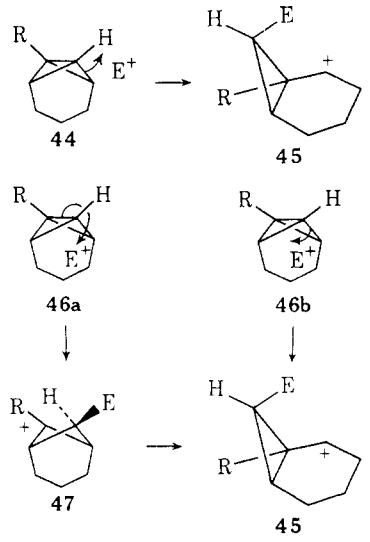
The Question of Directional Approach of Ag^+ to C_7. Findings detailed in earlier papers of this series have established that the catalyzed isomerizations of 1-substituted tricyclo[4.1.0.$0^{2,7}$]heptanes to 1,3-cycloheptadienes (the type α process) and to bicyclo[3.2.0]hept-6-enes (type γ rearrangement) proceed by initial attack of Ag^+ at the C_7 bridgehead carbon. Does this mechanistic dichotomy arise merely because of the approach of the transition metal ion from a direction above the fold of the bicyclobutane ring in one instance and from below the flap in the other? In this connection, Wiberg and Szeimies[13] have previously considered five different pathways for attack of a proton on a bicyclobutane ring and have calculated the relative energies of the several models. Symmetrical approach from above was favored for central bond cleavage while approach along the bisector of the $C_1C_2C_7$ angle seemed preferred for C_2–C_7 scission. Of these two options, however, only the latter (*i.e.*, **44** → **45**) corresponds to

(10) Z. Maksić, J. M. Jerkunica, and D. Stefanović, *Croat. Chim. Acta*, **38**, 49 (1966).

(11) G. L. Closs and L. E. Closs, *J. Amer. Chem. Soc.*, **85**, 2022 (1963).

(12) Similar exchange reactions have been studied previously: R. B. Larrabee, Ph.D. Thesis, The University of Chicago, 1967.

(13) K. B. Wiberg and G. Szeimies, *J. Amer. Chem. Soc.*, **92**, 571 (1970).



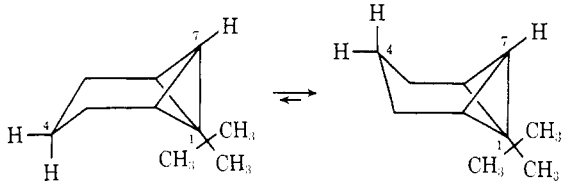
the stereospecificity of electrophilic bicyclobutane ring openings where retention of configuration occurs.[13,14]

As the electrophilic reagent becomes more sterically demanding, however, the situation is apt to become more intricate. Should attack occur by rupture of the C_2–C_7 bond with E^+ approaching along a path in or below the $C_1C_2C_7$ plane (as in **46b**) or by rearside attack at C_7 as in **46a**, the identical norcaranyl cation **45** would again be formed. Additionally, although this triad of mechanisms does account individually for product stereochemistry, they are oversimplified when considered in light of the nonclassical nature of cyclopropylcarbinyl cations.[15]

Extensive theoretical studies[16] have focused attention on the fact that although all the bicyclobutane carbon–carbon bonds are electron rich, the orbitals comprising the central bond alone possess exceedingly high levels (~96%) of p character. As a consequence of the small s content of these orbitals, large external lobes protrude below and behind the central bond and position appreciable electron density in this region. From the studies of Gassman[17] and Pomerantz[18] has emerged the recognition that various dienophiles and ene reagents exhibit an overwhelming preference for backside attack at the central bond. Thus, to the extent that neutral reagents manifest such high specificity for reaction from the underside direction, similar behavior is to be expected from electrophilic entities, particularly if steric shielding above the fold of the ring obtains.

With particular regard for the type γ rearrangement, four series of observations have bearing on the directionality of approach of the Ag^+ catalyst: (1) no bicycloheptene formation is witnessed unless at least a methyl group is situated at C_1; (2) a steady increase in the steric size of the C_1 alkyl group leads to a progressive diminution in α rearrangement with a concomitant increase in the amount of γ product; (3) the γ process is favored kinetically to a greater extent in 1,3-disubstituted tricycloheptanes when the C_3 group is disposed stereoproximally to the C_1 position; (4) 1,2-dimethyltricyclo[4.1.0.0^{2,7}]heptane (**6**) rearranges in the type γ mode to give only **7** and not **8**.

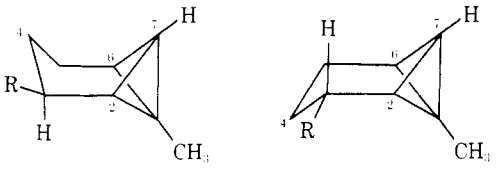
Although these data still lack the extent and variety to allow unequivocal conclusions to be drawn, certain trends are evident and suggestive of the gross orientational features associated with the γ rearrangement. For example, the behavior of 1-*tert*-butyltricyclo[4.1.0.0^{2,7}]heptane is not only such as to provide 92% bicycloheptene product (compared to 44% for the 1-methyl derivative), but also to rearrange more slowly than the methyl compound by a factor greater than 40-fold (Table I). In that ground-state conformation of this hydrocarbon which minimizes nonbonded interactions (**48b**), the size of the *tert*-butyl substituent is



48a 48b

seen to shield not only the upper surface of the hydrocarbon, but also to require that the C_4 methylene group be oriented predominantly toward C_7. This in effect serves to encumber approach of Ag^+ to C_7 from the rear side. The kinetic deceleration could result from this source or, equally plausibly, from the fact that approach to the side bonds flanking C_7 has become less facile. Since the edge bonds are recognized to be bent outward by as much as 33° [19] and somewhat distorted out of plane, the actual proximity of these orbitals to C_1 is not as great as representation **48b** would imply and could explain the observed rate retardation.

The regioselectivity exhibited by the 1,3-disubstituted tricycloheptanes can be interpreted as a further manifestation of the delicate balance between steric accessibility to the C_2C_7 or C_6C_7 edge bonds and product distribution. Here the stereodistal relationship of the groups aligns the trimethylene chain such that the C_4 atom is again positioned spatially near C_7 (*cf.* **49**). In



49 50

the stereoproximal examples, the equatorial demands of the R group at C_3 predispose C_4 in the opposite direction, thereby removing the steric component at C_7. As a result of this optimal conformational situation, more rapid rates of rearrangement are attainable in the latter examples.[1] It will be recalled also that the mag-

(14) (a) W. R. Moore, K. G. Taylor, P. Müller, S. S. Hall, and Z. L. F. Gaibel, *Tetrahedron Lett.*, 2365 (1970); (b) L. A. Paquette, G. R. Allen, Jr., and M. J. Broadhurst, *J. Amer. Chem. Soc.*, **93**, 4503 (1971); (c) W. G. Dauben and W. T. Wipke, *Pure Appl. Chem.*, **9**, 539 (1964).

(15) G. A. Olah, D. P. Kelly, C. L. Jeuell, and R. D. Porter, *J. Amer. Chem. Soc.*, **92**, 2544 (1970), and references cited therein.

(16) (a) M. Pomerantz and E. W. Abrahamson, *J. Amer. Chem. Soc.*, **88**, 2970 (1966); (b) K. B. Wiberg, *Tetrahedron*, **24**, 1083 (1968); (c) M. Pomerantz, G. W. Gruber, and R. N. Wilke, *J. Amer. Chem. Soc.*, **90**, 5040 (1968); (d) J. M. Schulman and G. J. Fisanick, *ibid.*, **92**, 6653 (1970); (e) M. D. Newton and J. M. Schulman, *ibid.*, **94**, 767 (1972); (f) D. R. Whitman and J. F. Chiang, *ibid.*, **94**, 1126 (1972).

(17) P. G. Gassman, *Accounts Chem. Res.*, **4**, 128 (1971), and references contained therein.

(18) M. Pomerantz, R. N. Wilke, G. W. Gruber, and U. Roy, *J. Amer. Chem. Soc.*, **94**, 2752 (1972).

(19) K. W. Cox, M. D. Harmony, G. Nelson, and K. B. Wiberg, *J. Chem. Phys.*, **50**, 1976 (1969).

nitude and direction of the regiospecificity exhibited by systems of type **49** and **50**[1] denote a greater propensity for formal C_6C_7 rupture irrespective of C_3 stereochemistry.

The results with **6** further develop these notions. By double substitution of a tricycloheptane nucleus at C_1 and C_2, access to the C_2C_7 bond by Ag^+ is apparently denied completely or at least to the extent that the C_6C_7 site becomes the exclusive center of attack for ultimate γ rearrangement. In evidence here is the clear trend that as a methyl group is moved from C_3 (syn or anti) to C_2, the level of effective steric influence increases appreciably.

These combined stereochemical and kinetic characteristics of the type γ rearrangement, although as yet not exhaustively developed, do provide some not wholly unreasonable basis for the proposal that approach of Ag^+ occurs either along one of the planes defined by $C_1C_2C_7/C_1C_6C_7$ from the C_7 direction or somewhat below this flap. Since the silver ion becomes transiently bonded to C_7, it will of necessity exhibit a greater proximity relationship to this atom during the attack.[20]

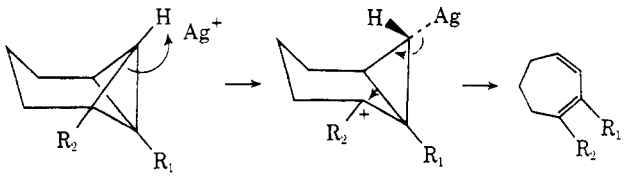
The capability of steric factors to effect reactivity imbalances is unquestionably of a high order. Utilization of their role to gain additional mechanistic information and to derive unifying predictions concerning reaction profiles is a goal which hopefully will emerge from studies currently being initiated.

So far we have been concerned with rearrangements that afford only bicycloheptenes. Somewhat by default, the picture that emerges for the type α rearrangement is one that would position the attacking Ag^+ above the planes defined by the two edge bonds flanking C_7 as in **44**. This mode corresponds to Wiberg's theoretical analysis of the preferred process for edge bond cleavage known to operate in the type α isomerization. The attachment of a substituent at C_1 could be responsible for precluding kinetically favored approach from this direction, except in those instances where the new substituent contains an atom or group of atoms capable of complexation to Ag^+. Confirmatory experimental proof for this assumption is difficult to provide, chiefly because such techniques as stereochemical labeling and the like lose their significance during conversion to the 1,3-cycloheptadiene product. Thus, a more complete dissection of the type α rearrangement pathway must await the formulation and execution of further experiments designed to shed new constructive light on this initial guiding premise.

Basis for the Cyclopropylcarbinyl–Cyclopropylcarbinyl Cation Rearrangement Concept. As the preceding discussion implies, some of the fruitful systems to examine for mechanistic elucidation should be those in which steric factors at least partially contradirect the normal processes and in which electronic contributions can be assessed without sacrificing some or all of the kinetic driving force. In this context, the 1-*tert*-butyl- (3:2:92:2) and 1-carbomethoxytricycloheptanes (96.6:1.9:0.4:0) comprise an exceedingly useful contrast. The relative rates of isomerization ($k_{overall}$) are such that the *tert*-butyl derivative rearranges 35 times faster than **10**. Consideration of the individual catalytic rate constants (k_i) for the α and γ rearrangements of these two substrates reveals that the rates of production of the 1,3-cycloheptadienes are essentially comparable (3.93×10^{-6} *vs.* 3.62×10^{-6} M^{-1} sec^{-1}). In contrast, the substituent effect on the type γ pathway causes a 1000-fold rate deceleration in the ester (1.20×10^{-4} *vs.* 1.40×10^{-7} M^{-1} sec^{-1})!

Given that the pathway to 1,3-cycloheptadienes does involve edge bond cleavage with formation of an argenticized cyclopropylcarbinyl cation[3,6,8,21] and that the working hypothesis featuring approach of Ag^+ unsymmetrically from above the flap is correct, the interpretation of these and related observations associated with the α process requires no additional assumptions. As outlined in Chart V, a concordant mechanism can

Chart V. A Detailed Mechanistic Interpretation of the Generalized Type α Rearrangement



R_2 = electron donating

be constructed to account not only for the apparent insensitivity to electronic effects, but also for the appreciable steric dependence of the pathway and the behavior of **6** which gives predominantly 1,2-dimethyl-1,3-cycloheptadiene.[3c] In brief, such cyclopropylcarbinyl cation formation leaves R_1 reasonably insulated from the developing electron-deficient center but is understandably sensitive to the nature of R_2. An inspection of molecular models shows that the accessibility of Ag^+ to the upper surface of the flap (despite the off-center approach) is facilitated progressively through the series *tert*-butyl < isopropyl ≪ methyl with the most abrupt modification occurring during the last structural modification. The catalytic rate constants reflect the situation rather clearly (3.93×10^{-6}, 1.71×10^{-5}, and 1.50×10^{-3} M^{-1} sec^{-1}, respectively).

Conforming to the prevailing reluctance of ester **10** for rearrangement along the bicycloheptene manifold and to the combined isotope data for several type γ processes, we conclude that concurrent weakening of the central and one side bond is likely operative in the activated complexes giving rise to this isomerization. In view of the nuclear geometry reported for bicyclobutane[19] and, by analogy, the tricyclo[4.1.0.0^{2,7}]-heptane system, it is readily perceived that attack of Ag^+ as considered in the previous section causes H_7 to undergo a substantial alteration of its relative molecular position while simultaneously experiencing hybridization and electronic changes of a high order.[22] These effects are expected to produce large force constant changes in this bond which, as a result of their syn-

(20) This orientation would be consistent with the greater electron density in the protruding orbital at C_7 and with the fact that a rapid and reversible equilibrium involving Ag^+ and the strained ring precedes rearrangement. Such considerations take a form which cause approach from somewhat below the flap to be more realistic since that region of space contains the almost pure p orbital in question.

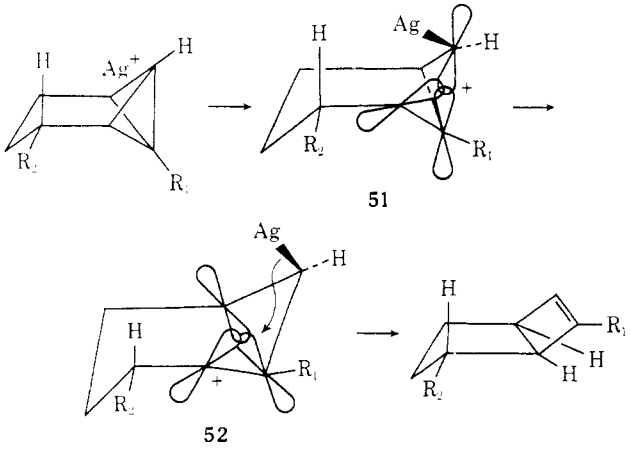
(21) (a) M. Sakai and S. Masamune, *J. Amer. Chem. Soc.*, **93**, 4610 (1971); (b) M. Sakai, H. H. Westberg, H. Yamaguchi, and S. Masamune, *ibid.*, **93**, 4611 (1971).

(22) Irrespective of whether Ag^+ approaches in-plane or below the flap, the C_7 stereochemistry of the intermediates is such that the covalently bonded metal becomes positioned on the endo face. This stereochemical outcome contrasts with that of the type α process where the covalently bonded Ag is exo disposed.

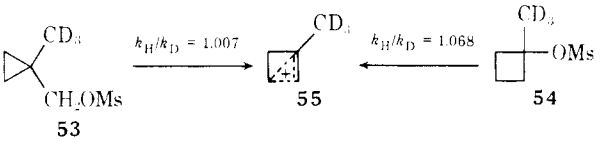
chronous operation, should induce appreciable kinetic deceleration upon C_7 deuterium substitution as is encountered.[6] The rather sizable magnitude of these isotope effects (k_H/k_D = 1.45–1.74) could arise from additive positive contributions due to several molecular perturbations. Firstly, a normal isotope effect is expected if, as is almost certainly the case, the transition state is "less rigid" or "looser" than the starting material.[23] Then there is a second significant vibrational change involving the C–H (D) twisting motion, the barrier for which would be lower in the protio derivative. In addition to this, the possibility of a "steric" isotope contribution[23,24] must be considered a real possibility; as Ag^+ approaches C_7, a congested situation develops away from which the C_7 hydrogen could rotate more rapidly than its deuterium counterpart. It is of course possible that other inter- and intramolecular effects are operative.[25] The three specific interactions discussed above would, however, all share in common the property of inducing positive and not inverse fractionation factors.

As illustrated in Chart VI, conversion of tricyclo-

Chart VI. A Detailed Mechanistic Interpretation of the Generalized Type γ Rearrangement



heptane **10** (R_1 = $COOCH_3$) to intermediate **51** would be energetically unfeasible relative to other rearrangement pathways which do not position some positive charge at C_1. In those examples where R_1 = CH_3 or CD_3, the formation of **51** would be favored, but hyperconjugative electron release from these substituents is expected to be negligible in view of the lack of an isotope effect encountered in solvolytic reactions involving cyclopropylcarbinyl cations substituted in like manner, *e.g.*, **55**.[26] Sunko and his coworkers have elegantly demonstrated that irrespective of whether the starting point is the cyclopropyl derivative **53** or cyclobutane **54**, only a very low level of hyperconjugative electron release is measurable. Accordingly, the behavior of **1**



in the present mechanistic context is adequately precedented.

The k_H/k_D values associated with the formation of **31** and **32** likewise correlate quite satisfactorily with whether the C_6C_7 (β effect) or C_2C_7 bond (α effect) is experiencing cleavage in the transition state.[23]

Cyclopropylcarbinyl–cyclopropylcarbinyl cation rearrangement of **51** under the usual stringent requirements of high stereochemical control[27] provides access to penultimate intermediate **52** which by ejection of Ag^+ as shown furnishes bicycloheptene in stereospecific fashion.[1] The completely stereospecific nature of cyclopropylcarbinyl–cyclopropylcarbinyl bond relocations has as its necessary consequence during the **51** → **52** change the positioning of H_2 and H_6 on that surface of the bicycloheptene framework which is cis to R_2. The stereochemical outcome of the Ag^+-catalyzed isomerization of 1,3-disubstituted tricycloheptanes[1] follows logically from this analysis. The entire sequence as outlined should (and is known to)[1] take place with little possibility for incursion of a near isoenergetic alternative pathway that would lead to loss of stereochemical integrity. In principle, this means that bicycloheptene stereomutations should not arise except under highly unusual conditions, and that regioselective control should be realizable by appropriate substitution of the trimethylene chain. This latter phenomenon has already been observed.[1,28]

Experimental Section

All boiling points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer and proton

(23) (a) C. J. Collins and N. S. Bowman, "Isotope Effects in Chemical Reactions," Van Nostrand-Reinhold, New York, N. Y., 1970; (b) E. A. Halevi, *Progr. Phys. Org. Chem.*, **1**, 109 (1963).

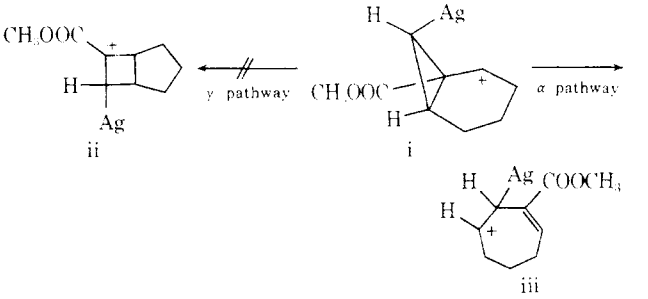
(24) (a) W. R. Dolbier, Jr., and J. H. Alonso, *J. Amer. Chem. Soc.*, **95**, 4421 (1973); (b) W. R. Dolbier, Jr., and S.-H. Dai, *ibid.*, **94**, 3946 (1972); (c) R. E. K. Winter and M. L. Honig, *ibid.*, **93**, 4616 (1971); (d) H. C. Brown and G. J. McDonald, *ibid.*, **88**, 2514 (1966); (e) K. Mislow, R. Graeve, A. J. Gordon, and G. H. Wahl, Jr., *ibid.*, **86**, 1733 (1964); (f) L. Melander and R. E. Carter, *ibid.*, **86**, 295 (1964); *Acta Chem. Scand.*, **18**, 1138 (1964).

(25) See, for example: D. D. Maness and L. D. Turrentine, *Tetrahedron Lett.*, 755 (1973); P. J. Stang and T. E. Dueber, *J. Amer. Chem. Soc.*, **95**, 2686 (1973).

(26) M. Nikoletic, S. Brocic, and D. E. Sunko, *Tetrahedron*, **23**, 649 (1967).

(27) For leading papers on this subject, see (a) ref 13; (b) ref 15; (c) Z. Majerski and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **93**, 665 (1971).

(28) It is indeed possible to argue that the isotope effect data should be interpreted with great reserve since its application to strained ring systems and particularly to metal-catalyzed isomerizations is still in its embryonic stages. While we concur with this general sense of caution, we are not willing to accept the position that useful mechanistic conclusions cannot be derived from the interpretation of secondary isotope effects in the absence of rigorous theoretical analysis. On this point, we do not stand alone.[23–25] This is particularly so when supportive kinetic and substituent effect data are also available. As an example of this inference, we cite the case of ester **10** whose inability to rearrange in significant amounts to bicycloheptene **12** cannot be construed (on the basis of *all* available evidence) as the result of the relative instability of ii and stability of iii. Although this suggestion may



seem feasible at first glance,[8] it soon loses its appeal because of the requirement that intermediate i be common to both the α and γ processes. Rather, the present and earlier deuterium isotope effect studies attest reliably to the fact that nonidentical kinetically controlled reactions occur to produce intermediates of necessarily different structure.

magnetic resonance spectra were recorded with Varian A-60A and HA-100 spectrometers as well as a Joelco MH-100 instrument. Apparent splittings are given in all cases. Mass spectra were obtained with a CEC-MS9 instrument at an ionization potential of 70 eV. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. Preparative and rough analytical vpc work was done on a Varian Aerograph A90-P3 instrument equipped with a thermal conductivity detector. Refined product composition data were obtained with the aid of a Hewlett-Packard 5750 unit (flame ionization detector) equipped with an electronic integrator.

1-Carbomethoxytricyclo[4.1.0.0^{2,7}]heptane (10). Tetramethylethylenediamine (380 mg, 3.3 mmol) was added in a nitrogen atmosphere to a magnetically stirred solution of *n*-butyllithium (3.3 mmol) in hexane (1.5 ml) which was cooled to 5°. A solution of **9**[29] (310 mg, 3.3 mmol) in pentane (1 ml) was added and the mixture was stirred at room temperature for 24 hr. Pentane (1 ml) was added to the reaction mixture and the slurry was removed by syringe and added during 5 min to a magnetically stirred solution of methyl chloroformate (4.0 g, 43 mmol) in pentane (2 ml) at 5°. After completion of the addition, the mixture was stirred at 5° for 15 min before dilution with pentane (20 ml) and suction filtration. The filtrate was concentrated at reduced pressure (100 mm) and the residue, which was diluted with pentane (5 ml), was vigorously stirred with 10% aqueous sodium bicarbonate solution (3 ml). The separated organic layer was washed twice with saturated cupric sulfate solution (5 ml), dried, and reconcentrated at 100 mm. Preparative vpc isolation (column A,[30] 120°) of **10** from the residue furnished 100 mg (25%) of pure colorless oil: ν_{max}^{neat} 2900, 1720, 1280, 1190, 1165, 1140, 1075, and 748 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 3.68 (s, 3, OCH_3), 3.25–3.07 (m, 2, H_2 and H_6), 2.25 (t, J = 3.5 Hz, 1, H_7), and 1.60–1.30 (m, 6, methylenes).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.11; H, 8.22.

Preparative Scale Ag$^+$-Catalyzed Rearrangement of 10. An anhydrous benzene solution (0.5 ml) of **10** (74 mg, 0.49 mmol) and $AgClO_4$ (0.089 mmol) was heated in a sealed nmr tube at 72 ± 1° which was removed periodically for pmr analysis. After a total of 66 hr, no **10** was detectable and the reaction mixture was quenched by shaking with a mixture of saturated aqueous sodium chloride solution (2 ml) and pentane (0.5 ml). The separated aqueous layer was washed with pentane (1 ml) and the combined organic layers were analyzed by vpc (column B,[30] 128°). In their order of elution, the rearrangement products were identified as **12** (0.4%), **13** (1.9%), and **11** (96.6%) by comparison of retention times with those of authentic samples. An unknown product (1.1%) appeared as a peak between **12** and **13**. No **16** was detected. Preparative vpc (column A,[30] 110°) yielded 29 mg (40%) of analytically pure **11**. Its spectra were identical with those of the authentic sample (*vide infra*).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.80; H, 8.00.

1- and 2-Carbomethoxy-1,3-cycloheptadienes. A solution of *n*-butyllithium (5.1 mmol) in hexane (2.3 ml) was added dur r g 5 min to a magnetically stirred solution of a *ca.* 60:40 mixture of 2- and 1-bromo-1,3-cycloheptadiene[31] (800 mg, 4.6 mmol) in ether (8 ml) at 5° under a nitrogen atmosphere. After the resultant solution was stirred at 5° for 1 hr and at room temperature for 5 hr, it was removed by syringe and added over a 5-min period to a magnetically stirred solution of methyl chloroformate (7.52 g, 0.08 mol) in ether (10 ml) at 5°. After 30 min at this temperature, the mixture was allowed to warm to room temperature, diluted with pentane (25 ml), and filtered. The filtrate was concentrated at 100 mm without heating, diluted with pentane (25 ml), washed with 5% sodium bicarbonate solution (25 ml), dried, and concentrated at 100 mm. Subsequent preparative vpc (column C,[30] 145°) of the residue furnished 5 mg of the 1 isomer (t_r = 6.5 min) and 20 mg of **11** (t_r = 7.7 min), which were present in a 30:70 ratio. This sample of **11** exhibited identical vpc retention times and pmr spectrum with that of the above rearrangement product.

For **11**: $\delta_{TMS}^{CDCl_3}$ 7.34–6.93 (m, 1, olefinic), 6.59–5.72 (m, 2, olefinic), 3.78 (s, 3, OCH_3), 2.83–2.0 (m, 4, allylic), and 2.0–1.60 (m, 2).

For the 1 isomer: $\delta_{TMS}^{CDCl_3}$ 6.42–5.74 (m, 3, olefinic), 3.84 (s, 3, OCH_3), 2.90–2.42 (m, 4, allylic), and 2.14–1.92 (m, 2). For $C_9H_{12}O_2$ *m/e* 152.0839 (calcd *m/e* 152.0837).

6-Carbomethoxybicyclo[3.2.0]hept-6-ene (12). An ether solution (2 ml) of **11** (12 mg) was placed in a stoppered quartz test tube and was irradiated for 7 hr at 5° with a 450-W Hanovia lamp using a water-cooled Pyrex immersion well. Vpc analysis (column C,[30] 115°) indicated that no **11** remained and that two components were present with retention times of 5.9 (24%) and 8.9 min (76%). The slower eluting major component was collected (5.3 mg, 44%) by preparative vpc on column A (115°) and was identified as **12** from its characteristic pmr spectrum: $\delta_{TMS}^{CDCl_3}$ 6.66 (s, 1, olefinic), 3.73 (s, 3, OCH_3), 3.56–3.26 (m, 1, bridgehead), 3.26–2.94 (m, 1, bridgehead), and 2.19–0.94 (m, 6, methylenes). For $C_9H_{12}O_2$ *m/e* 152.0839 (calcd *m/e* 152.0837).

***syn*- and *anti*-1-Carbomethoxymethylidenecyclohex-2-ene (13 and 16).** A solution of carbomethoxymethylenetriphenylphosphorane[32] (1.4 g, 4.2 mmol) and 2-cyclohexenone (420 mg, 4.0 mmol) in dry benzene (10 ml) was refluxed for 15 hr after which time no reaction was detected. Toluene (5 ml) and additional enone (800 mg, 7.6 mmol) were introduced and the benzene was removed by distillation. The reaction mixture was refluxed for 48 hr, cooled to 25°, diluted with pentane (100 ml), and filtered. After removal of pentane on a rotary evaporator, the residual toluene solution was flash-vacuum distilled (110° (0.1 mm)) with collection of all volatiles at −80°. Preparative vpc of the distillate (column D,[30] 145°) allowed collection of a slower eluting major component (40 mg, t_r = 9.8 min, 70%) and a faster eluting minor component (15 mg, t_r = 7.7 min, 30%) which were identified as **16** and **13**, respectively, on the basis of their pmr spectra.

For **13**: $\delta_{TMS}^{CDCl_3}$ 6.27–6.10 (m, 2, ring olefinic), 5.60 (br s, 1, vinyl), 3.70 (s, 3, OCH_3), 3.15–2.84 (m, 2, H_6), 2.55–2.05 (m, 2, H_4), and 2.05–1.58 (m, 2, H_5). For $C_9H_{12}O_2$ *m/e* 152.0839 (calcd *m/e* 152.0837).

For **16**: $\delta_{TMS}^{CDCl_3}$ 7.50 (d with fine splitting, J = 10 Hz, 1, H_2), 6.45–6.05 (m, 1, H_3), 5.51 (br s, 1, vinyl), 3.68 (s, 3, OCH_3), 2.60–2.07 (m, 4, allylic), and 2.07–1.53 (m, 2, H_5).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.66; H, 7.97.

Kinetic Analysis of the Rearrangement of 10. The previously described[4] general procedure for pmr kinetic analyses of $AgClO_4$-catalyzed rearrangements of substituted tricyclo[4.1.0.0^{2,7}]heptanes was followed. Five data points were collected over a period of 11 days (*ca.* 35% conversion) with a pure sample of **10** (15 mg, 0.1 mmol) in $AgClO_4$–anhydrous benzene (0.300 ml of 0.179 *M*) maintained at 40.0 ± 0.1°. Comparison of the relative integrated signal intensities for the H_2/H_6 (wing) proton multiplet of **10** *vs.* the combined overlapping CO_2CH_3 singlet signals due to **10** and **11** with time and application of statistical corrections followed by the usual data treatment led to the average catalytic rate constant given in Table I.

Vpc Kinetic Analyses of the $AgClO_4$-Catalyzed Rearrangement of Tricyclo[4.1.0.0^{2,7}]heptanes 18–21, 29, and 39. Solutions of silver perchlorate in benzene were prepared by dilution of an anhydrous pretitrated standardized stock solution (0.1877 *M*) with dry benzene. Into an ammonium hydroxide washed, predried, 1-dram screw-cap glass vial equipped with an air-tight rubber septum (which had been presoaked in benzene for *ca.* 2 min) was injected 1.00 ml of the $AgClO_4$–benzene solution and equilibration was achieved in a Sargent-Welch constant-temperature circulating water bath preset and maintained at 40.0 ± 0.1° for 30 min. The substrate (0.015–0.030 ml) was subsequently injected with a 0.100-ml syringe, with simultaneous initiation of an electric timer and vigorous swirling of the reaction vial for 60 sec. Aliquots (*ca.* 0.1 ml) were withdrawn by means of a syringe at appropriate time intervals (360–1800 sec), injected into a mixture of saturated aqueous sodium chloride solution (1.5 ml) and pentane (0.25 ml), noting the elapsed reaction time, and then vigorously shaken for 60 sec before storage at 0° for subsequent vpc analysis using column

(29) W. R. Moore, H. R. Ward, and R. F. Merritt, *J. Amer. Chem. Soc.*, **83**, 2019 (1961).

(30) The following vpc columns of Al tubing were utilized in the course of this study: A, 6 ft × 0.25 in. 5% SE-30 on 60–80 mesh Chromosorb G; B, 10 ft × 0.125 in. 2% Carbowax 20M on 60–80 mesh Chromosorb G; C, 6 ft × 0.25 in. 5% DEGS on 60–80 mesh Chromosrob G; D, 6 ft × 0.25 in. 5% XF-1150 on 60–80 mesh Chromosorb G; E, 10 ft × 0.125 in. 10% Carbowax 20M on 60–80 mesh Chromosorb G; F, 24 ft × 0.125 in. 1% SE-30 Hewlett-Packard "high-efficiency" column; G, 12 ft × 0.25 in. 5% Carbowax 20M on NaOH-washed Chromosorb P (60–80 mesh); H, 3 ft × 0.25 in. 5% Carbowax 20M on 60–80 mesh Chromosrob G; I, 12 ft × 0.25 in. 5% OV-11 on 60–80 mesh Chromosorb G.

(31) D. G. Lindsay and C. B. Reese, *Tetrahedron*, **21**, 1673 (1965).

(32) Prepared from carbomethoxymethyltriphenylphosphonium chloride according to a procedure analogous to that reported by O. Isler, H. Gutmann, M. Montavon, R. Rüegg, G. Ryser, and P. Zeller [*Helv. Chim. Acta*, **40**, 1242 (1957)], who used the bromide salt.

E[30] (68°). In each run a total of five aliquots were withdrawn, and the remainder was kept at 40.0 ± 0.1° until complete (≥99.9%) rearrangement had occurred, after which time it was quenched and then stored as above for vpc analysis of the product ratios using column F[30] (80°). All vpc analyses were performed with a Hewlett-Packard Model 5750 instrument in the flame-ionization mode. Peak areas were obtained with a Hewlett-Packard Model 3370A Integrator; due to lack of sufficient quantities of certain products, suitable peak response corrections were not made in all cases. Appropriate controls excluded the possibility of rearrangement during vpc analysis under the stated conditions.

The vpc peak area for bicyclo[3.2.0]hept-6-ene products in a given aliquot was divided by the percentage of these compounds in the corresponding final product distribution, thus giving a calculated value for the area of all products ($Area_P$) in the aliquot. The sum of $Area_P$ and the corresponding vpc peak area for starting material ($Area_{SM}$) was divided by $Area_{SM}$, and a plot of $\ln[(Area_P + Area_{SM})/Area_{SM}]$ *vs.* time yielded a straight line from which $k_{overall}$ = slope/[$AgClO_4$].

For measurement of the kinetic isotope effects for individual bicycloheptene isomers, the following procedure was adopted. After 36 hr of reaction as above, the reaction mixture was quenched with a saturated aqueous solution of sodium chloride (2 ml) diluted with pentane (0.5 ml). The organic layer was subjected to preparative vpc (column G,[30] 100°) and the bicycloheptene mixture was collected. The above procedure was repeated simultaneously using **29** and **39** and the various vpc samples were separately dissolved in C_6D_6–10% TMS (0.25 ml) and their nmr spectra (Varian HA-100) recorded in the H_2 methine region. Two traces for each sample were then Xeroxed five times and the individual H_2 absorptions for the 6- and 7-methyl isomers were cut out and weighed. For **21**, the distribution of type γ products was 68 and 22.7%, respectively, whereas for **29** the quantity of **31** and **32** produced was 73.4 and 18.3%. The isotope effects were calculated as follows: for **21**, $k_\gamma = 4.63 (\pm 0.02) \times 10^{-4}\ M^{-1}\ sec^{-1}$ and therefore $k_{(6\text{-Me})} = (4.63 \times 10^{-4})(0.68) = 3.15 \times 10^{-4}\ M^{-1}\ sec^{-1}$ and $k_{(7\text{-Me})} = (4.63 \times 10^{-4})(0.227) = 1.05 \times 10^{-4}\ M^{-1}\ sec^{-1}$; for **29**, $k_\gamma = 4.96 (\pm 0.12) \times 10^{-4}\ M^{-1} sec^{-1}$ and therefore $k_{31} = (4.96 \times 10^{-4})(0.734) = 3.64 \times 10^{-4}\ M^{-1}\ sec^{-1}$ and $k_{32} = (4.96 \times 10^{-4})(0.183) = 0.908 \times 10^{-4}\ M^{-1}\ sec^{-1}$. Thus, k_H/k_D for **29** → **31** = $3.15 \times 10^{-4}/3.64 \times 10^{-4} = 0.87 \pm 0.05$ and k_H/k_D for **29** → **32** = $1.05 \times 10^{-4}/0.908 \times 10^{-4} = 1.17 \pm 0.14$. A comparable analysis was made for **39**.

2-Bromo-3-ethoxy-2-cyclohexen-1-one (23).[33] With protection from excess light, a magnetically stirred solution of 3-ethoxy-2-cyclohexen-1-one (**22**)[34] (46.2 g, 0.330 mol) in carbon tetrachloride (200 ml) was gradually treated (*ca.* 1 hr) with recrystallized *N*-bromosuccinimide (59.8 g, 0.336 mol), using a chilled water bath for cooling. After complete addition, the mixture was stirred for 1 hr and solvent was removed on a rotary evaporator. The solid residue was quickly swirled with 10% sodium carbonate solution, and the remaining solid, which was collected by suction filtration, was washed twice with 50-ml portions of water. The semidry solid was immediately dissolved in hot carbon tetrachloride (225 ml), filtered through a cone of anhydrous sodium sulfate, and cooled. There was obtained 49.5 g (68%) of **23** as white flakes, mp 95–101°: $\delta_{TMS}^{CDCl_3}$ 4.20 (q, J = 7 Hz, 2, OCH_2CH_3), 2.85–2.30 (m, 4, methylenes), 2.30–1.70 (m, 2, methylene), and 1.42 (t, J = 7 Hz, 3, CH_3).

Attempted recrystallization of a portion of this sample of **23** from hot carbon tetrachloride led to decomposition[35] with formation of 2-bromo-1,3-cyclohexanedione, mp 163–164° (from hexane–chloroform) (lit.[36] mp 162–164°).

2-Bromo-3-methyl-2-cyclohexen-1-one (24). An ether solution (200 ml) of methylmagnesium iodide [prepared from magnesium turnings (6.1 g, 0.25 g-atom) and methyl iodide (35.5 g, 0.25 mol) in the usual manner] was transferred to a dropping funnel from which it was added dropwise to a mechanically stirred solution of **23** (51.9 g, 0.237 mol) in anhydrous tetrahydrofuran (525 ml) at such a rate as to maintain the reaction mixture at *ca.* 40–50°. After complete addition, the reaction mixture was stirred at *ca.* 45–50° for 1 hr, cooled to room temperature, and treated with saturated aqueous ammonium chloride solution (450 ml). Water (50 ml) was added to dissolve solids and stirring was continued for 30 min. The separated aqueous layer was washed with ether (250 ml) and the combined organic layers were washed with saturated sodium chloride solution (175 ml) before drying. Solvents were removed without heating on a rotary evaporator giving 48.6 g of crude **24** as an orange oil (theoretical yield = 44.8 g), which was used without further purification.

Treatment of **24** with 2,4-dinitrophenylhydrazine in the usual manner[37] yielded the dinitrophenylhydrazone of **24**, mp 163° dec (lit.[36] mp 164–165° dec).

2-Bromo-3-methyl-2-cyclohexen-1-ol (25). An ether solution (110 ml) of the crude **24** (48.6 g) was added dropwise to an ice-cooled, magnetically stirred suspension of lithium aluminum hydride (5.3 g) in ether (210 ml) over a period of 1 hr, after which time stirring and cooling were continued for 15 min, before sequential addition of water (5.3 ml), 20% sodium hydroxide solution (5.3 ml), and more water (16 ml). The pink solids were collected by suction filtration and washed four times with 200-ml portions of ether. The combined ether solutions were dried and concentrated to give 34.6 g of crude **25** as a brown oil, which was subsequently converted to its methyl ether (**26**) without further purification.

For **25**: $\delta_{TMS}^{CDCl_3}$ 4.45–4.10 (m, 1, H_1), 2.75 (br s, 1, OH), 2.60–1.50 (m, 6, methylenes), and 1.83 (s, 3, CH_3).

For $C_7H_{11}O^{79}Br$ *m/e* 189.9992 (calcd *m/e* 189.9994).

2-Bromo-3-methoxy-1-methylcyclohexene (26). A dimethylformamide (100 ml) solution of crude **25** (34 g) was added dropwise to a magnetically stirred suspension of sodium hydride (8.6 g) in dimethylformamide (200 ml) at ambient temperature (exothermic). Following cessation of hydrogen evolution, the brown reaction mixture was chilled in an ice bath before the dropwise addition of methyl iodide (260 g). After complete addition and continued stirring at ice bath temperature for 2 hr, the reaction mixture was treated with water (400 ml) and extracted with pentane (400 ml). The separated aqueous layer was extracted with pentane (400 ml), and the combined pentane layers were washed four times with 100-ml portions of water, dried, and evaporated. The residue orange oil was distilled to give 12.3 g (25% overall from **23**) of **26** (90% purity), bp 30–65° (0.3–0.5 mm). Preparative vpc purification of a small sample (column H,[30] 105°) gave pure **26** as a colorless oil; $\delta_{TMS}^{CDCl_3}$ 3.80 (br s, 1, H_1), 3.42 (s, 3, OCH_3), 2.35–1.40 (m, 6, methylenes), and 1.83 (s, 3, CH_3). For $C_8H_{13}O^{79}Br$ *m/e* 204.0153 (calcd *m/e* 204.0150).

Anal. Calcd for $C_8H_{13}BrO$: C, 46.85; H, 6.39. Found: C, 47.18; H, 6.35.

2-Deuterio-3-methoxy-1-methylcyclohexene (27). A magnetically stirred solution of distilled **26** (12 g, *ca.* 0.05 mol) in anhydrous ether (300 ml) was cooled under nitrogen to −78° and a solution of *n*-butyllithium in hexane (30 ml of 2.25 *M*, 0.067 mol) was added dropwise over a 20-min period. Following complete addition and continued stirring at −78° for 1 hr, the cooling bath was removed and the reaction mixture was allowed to warm slowly (45 min) to 0°. Deuterium oxide (15 ml, 0.75 mol) was added and stirring at ice-bath temperature was continued for 45 min. After addition of water (150 ml) and extraction with ether (300 ml), the separated organic layer was washed with saturated sodium chloride solution (50 ml) and dried. The solvent was removed by distillation using a 6-in. Vigreux column leaving a residue of crude **27** as a fragrant yellow oil for subsequent conversion to **28** without further purification. Preparative vpc (column I,[30] 100°) gave pure **27**, the nmr spectrum of which indicated essentially complete (≥95%) deuterium incorportaion at the vinyl position: $\delta_{TMS}^{CDCl_3}$ 3.70 (m, 1, H_1), 3.34 (s, 3, OCH_3), 2.10–1.34 (m, 6, methylenes), and 1.68 (br s, 3, CH_3). For $C_8H_{13}OD$ *m/e* 127.1109 (calcd *m/e* 127.1107).

7,7-Dibromo-2-methoxy-6-methylbicyclo[4.1.0]heptane-*1-d* (28). Reaction of crude **27** with bromoform and potassium *tert*-butoxide was carried out according to the predescribed procedure.[1] The overall yield of **28** beginning from **26** was 46%. The nmr spectrum of **28** was consistent with its assigned structure, and was very similar to that of its protium analog.[1]

At an ionizing voltage of 70 eV, no parent ion isotope cluster at *m/e* 297, 299, and 301 was detectable; however, a *ca.* 1:2:1 isotope cluster at *m/e* 265, 267, and 269 was present, presumably due to loss of methanol and formation of $C_8H_9DBr_2$ ions. For $C_8H_9D^{79}Br_2$ *m/e* 264.9216 (calcd *m/e* 264.9213).

(33) This reaction was based on the reported similar preparation of the 3-methoxy analog of **13** by I. N. Nazarov and S. I. Zav'yalov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 639 (1959).

(34) W. F. Gannon and H. O. House, *Org. Syn.*, **40**, 41 (1960).

(35) The instability of 2-bromo-3-methoxy-2-cyclohexen-1-one toward hydrolysis to 2-bromo-1,3-cyclohexanedione has been noted.[33]

(36) I. N. Nazarov and S. I. Zav'yalov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 186 (1958).

(37) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," 3rd ed, Wiley, New York, N. Y., 1948, p 171, procedure 15.

Reaction of 28 with Methyllithium. Cyclization of **28** with methyllithium was performed according to the procedure previously described for the protio analog.[1] There was obtained in 60% combined yield a mixture of **29** (66%) and **30** (34%) which were readily separable by preparative vpc (column G,[30] 100°).

For **29**: $\delta_{TMS}^{C_6D_6}$ 3.40–3.00 (m, 1, H_6), 3.17 (s, 3, OCH_3), 2.08 (br s with fine splitting, 1, H_3), 1.85–1.20 (m, 4, methylenes), 1.49 (s, 3, CH_3), and 1.13 (br s with fine splitting, 1, H_7). For $C_9H_{13}OD$ *m/e* 139.1105 (calcd *m/e* 139.1107).

For **30**: $\delta_{TMS}^{C_6D_6}$ 3.62 (d, J = 7 Hz, 1, H_2), 3.02 (s, 3, OCH_3), 2.50 (v br d, J = 7 Hz, 1, H_3), 1.02 (s, 3, CH_3), and 2.3–1.4 (m, 5). For $C_9H_{13}OD$ *m/e* 139.1105 (calcd *m/e* 139.1107).

***syn*-3-Methoxy-1-methyltricyclo[4.1.0.0^{2,7}]heptane-7-*d* (39).** An anhydrous solution of sodium methoxide in methanol-*O-d* was prepared by dissolving sodium (300 mg, 13 mg-atoms) in methanol-*O-d* (7 ml), and an aliquot (3 ml) of this stock solution together with **21** (295 mg, 2.14 mmol) was sealed in a base-washed glass tube under vacuum. After heating at *ca.* 135–140° for 66 hr, the cooled reaction mixture was treated with water (15 ml) and extracted three times with 10-ml portions of pentane. The combined pentane layers were dried and concentrated by slow distillation using a 6-in. Vigreux column to give a residual oil which was subjected to preparative vpc (column G,[30] 100°). There was isolated a 41% yield of **39**: $\delta_{TMS}^{C_6D_6}$ 3.35–3.02 (m, 1, H_3), 3.22 (s, 3, OCH_3), 2.39 (apparent dd, 1, H_2), 2.08 (m, 1, H_6), 1.90–0.98 (m, 4, methylenes), and 1.50 (s, 3, CH_3). Absence of detectable absorption at *ca.* δ 1.40 confirmed that virtually complete deuteration of the 7-bridge position had occurred. From mass spectral data, deuterium incorporation into **39** was calculated to be $\geq$96% complete. For $C_9H_{13}OD$ *m/e* 139.1105 (calcd *m/e* 139.1107).

For **42/43**, the pmr spectrum (in C_6D_6) was very similar to that previously reported for the unlabeled mixture[1] except that no detectable olefinic absorption was seen in the δ 5.5 region. For $C_9H_{13}DO$ *m/e* 139.1109 (calcd *m/e* 139.1107).

These pmr features contrast with those recorded for the **31/32** mixture obtained from the rearrangement of **29**: $\delta_{TMS}^{C_6D_6}$ 5.47 (br s with additional fine splitting, 1, olefinic), 3.50–3.30 (2 m in 20:80 ratio, 1, H_2), 3.25–2.85 (m, 1, bridgehead), 3.10 (s, 3, OCH_3), 2.15–1.15 (m, 4, methylenes), and 1.44 (t, J = 1.5 Hz, 3, CH_3). For $C_9H_{13}DO$ *m/e* 139.1105 (calcd *m/e* 139.1107).

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Kinetics of Inactivation of α-Chymotrypsin with Substituted Benzenesulfonyl Fluorides

J. T. Gerig* and D. C. Roe

Contribution from the Department of Chemistry, University of California, Santa Barbara, Santa Barbara, California 93106. *Received August 2, 1973*

Abstract: The inactivation of α-chymotrypsin by a series of fluoro- and trifluoromethyl-substituted benzenesulfonyl fluorides is described. A technique based upon displacement of the dye Biebrich Scarlet from its complex with the enzyme was used to follow the kinetics of the inactivation reaction; in favorable systems this method gives both the binding constant of the irreversible inhibitor (K_I) and the rate constant for covalent bond formation (k_r) in a single experiment. These data are presented and discussed.

Recent nmr studies of the interaction of α-chymotrypsin (CT) with competitive inhibitors have yielded new information regarding the nature of the complexes formed.[1-9] These various applications of nmr techniques to the study of the interactions between CT and substrate-sized molecules suggest that nmr methods might profitably be employed in examination of the acylenzyme intermediate thought to be involved in CT catalysis.[10,11] Many acylchymotrypsins are not stable enough at ordinary temperatures to be observed conveniently in nmr experiments although a recent report suggests that the prospects for these experiments could be improved by operating at subzero temperatures in mixed solvents.[12] However, sulfonyl fluorides have been shown to yield acylenzyme analogs that are stable for long periods of time except at high pH,[13-16] and one of these derivatives, tosylchymotrypsin, has been studied by X-ray crystallographic methods.[17,18] With the hope that nmr studies of the corresponding proteins in solution may ultimately be compared to crystal structure data we have prepared a series of fluoro- and trifluoromethyl-substituted benzenesulfonyl fluorides designed to probe the hydrophobic binding site of CT.[15] The synthesis of these materials and a study of the kinetics of their reactions with this enzyme are reported here; a subsequent paper will deal with nmr studies of the derivatized enzymes.[19]

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