

Kinetic mechanism for dimerization of an α -thioamide substituted benzyl carbocation in aqueous solution

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Received 20 October 1997; revised 29 December 1997; accepted 2 January 1998

ABSTRACT: The products of reaction of the α -(*N,N*-dimethylthiocarbamoyl)-4-methoxybenzyl carbocation (1^+) intermediate of solvolysis of α -(*N,N*-dimethylthiocarbamoyl)-4-methoxybenzyl benzoate esters ($1\text{-O}_2\text{CAr}$) show a strong dependence on solvent. The only product from reaction in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) is 2-dimethylamino-6-methoxybenzothiophene (**2**) from intramolecular cyclization of 1^+ . The reaction of 1^+ in 50:50 (v/v) methanol–water ($I = 0.50$, NaClO_4) gives mainly the adducts to solvent. In 50:50 (v/v) trifluoroethanol–water ($I = 0.50$, NaClO_4), 1^+ partitions between reaction with solvent (k_s , 27% yield), cyclization to form **2** (k_c , 3% yield) and nucleophilic addition of **2** to 1^+ (k_{alk} , 70% yield) to form dimeric product **3**. The yield of **3** in 50:50 (v/v) trifluoroethanol–water ($I = 0.50$, NaClO_4) is independent of the leaving group at $1\text{-O}_2\text{CAr}$ and remains constant as the concentration of the substrate is increased fourfold. These data show that the rate-determining step for dimerization of $1\text{-O}_2\text{CAr}$ is ionization of substrate to form 1^+ and that the products of the reaction are determined by the rate constant ratio for partitioning of 1^+ between addition of solvent and cyclization. The rate constant ratios determined for the partitioning of 1^+ in 50:50 (v/v) trifluoroethanol–water ($I = 0.50$, NaClO_4) were $k_s/k_c = 0.8 \text{ M}^{-1}$ and $k_{\text{alk}}/k_s = 540\,000 \text{ M}^{-1}$. © 1998 John Wiley & Sons, Ltd.

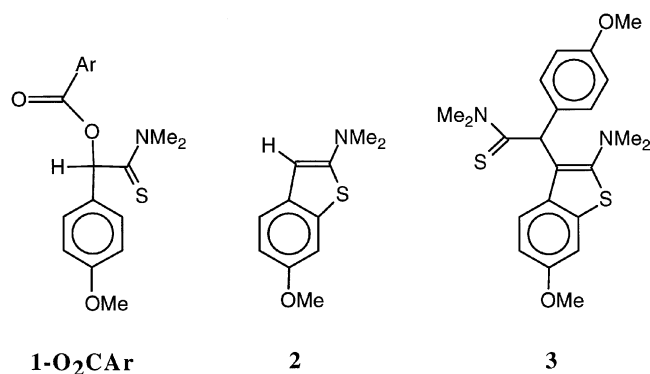
KEYWORDS: carbocation; thioamide; kinetics

INTRODUCTION

We recently reported that the reaction of α -(*N,N*-dimethylthiocarbamoyl)-4-methoxybenzyl pentafluorobenzoate ($1\text{-O}_2\text{C}_6\text{F}_5$) in mixed aqueous organic solvents proceeds by a $D_N + A_N$ (S_N1) mechanism through an α -thioamide-substituted 4-methoxybenzyl carbocation intermediate 1^+ .¹ We were very surprised to observe conversion of the carbocation 1^+ to **2** and then to the dimeric product **3** in a total yield of ca 70% because, to the best of our knowledge, there is no precedent in organic chemistry for dimerization of the extremely low steady-state concentrations [$<10^{-8} \text{ M}$, see Discussion] of the strongly electrophilic species 1^+ in a nucleophilic aqueous solvent.²

We report here the results of a study of the effects of changing solvent, substrate concentration and substituted benzoate leaving group on the products of the reaction of $1\text{-O}_2\text{CAr}$ and the time course for formation of the products in 50:50 (v/v) trifluoroethanol–water ($I = 0.50$, NaClO_4) (see Scheme 1). The experimental results define the rate-determining and product-determining steps for the dimerization of 1^+ and the rate constant ratios for

partitioning of 1^+ between intramolecular cyclization to **2**, nucleophilic addition of solvent and nucleophilic addition of alkene **2**.



EXPERIMENTAL

Materials. HPLC-grade methanol was purchased from Fisher and HPLC-grade acetonitrile and Gold label-grade 2,2,2-trifluoroethanol from Aldrich. Water was purified by distillation and passage through a Milli-Q purification system. All other organic chemicals used for syntheses were of reagent grade and were used without further purification.

Syntheses. The methods for the preparation of α -(*N,N*-

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Contract/grant sponsor: National Institutes of Health; contract grant number: GM 39754.

dimethylthiocarbamoyl)-4-methoxybenzyl pentafluorobenzoate (**1-O₂CC₆F₅**) and α -(*N,N*-dimethylthiocarbamoyl)-4-methoxybenzyl 4-nitrobenzoate (**1-O₂CC₆H₄-4-NO₂**) were described in a recent paper.¹

HPLC product analyses. Product analyses were carried out at room temperature ($22 \pm 2^\circ\text{C}$). The reactions were initiated by making a 100-fold dilution of substrate in acetonitrile to give a final concentration of 0.05–0.2 mM. The procedures for HPLC analyses were as described in earlier work,^{3,4} except that the mixed methanol–water solvent used to elute the products of the reaction of **1-O₂CC₆F₅** in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) was prepared by mixing methanol and water which contained 0.1 M sodium carbonate (pH 9) to give a final concentration of 10 mM buffer. The buffered aqueous phase was used because **2** appears to be unstable under these conditions to elution with unbuffered solutions of methanol–water. The fractional yield of **2** observed for reaction in other solvents was not affected by addition of this buffer.

The products of the reaction of **1-O₂CAr** were monitored at 271 nm, which is λ_{max} for **1-OH**. The procedures for identification of the reaction products have been described in earlier work.^{1,2} The products of the reaction of **1-O₂CC₆F₅** were determined after completion of the reaction (*ca* 10 half-times), and the products of the reaction of **1-O₂CC₆H₄-4-NO₂** were determined after a reaction time of 30 hours (*ca* six half-times). The ratios of the yields of products were calculated from the ratios of their peak areas from HPLC analysis and the ratios of their extinction coefficients.² In cases where 1 mol of substrate **1-O₂CAr** reacts to form 1 mol of product **1-OSolv** or **2**, the fraction of the maximum theoretical product yield was calculated using Eqn 1 where $A_{1-\text{OSolv}}$, A_2 and A_3 refer to the areas of the respective product peaks from HPLC analysis and $\epsilon_{1-\text{OSolv}} = 13000$,

$\epsilon_2 = 11200$ and $\epsilon_3 = 22000 \text{ M}^{-1} \text{ cm}^{-1}$ are the extinction coefficients of these products at 271 nm.² The fraction of the theoretical yield of the dimer **3** was calculated using Eqn (2). The terms in the numerator of Eqns (1) and (2) are proportional to the moles of product formed, while the term in the denominator $[A_{1-\text{OSolv}}/\epsilon_{1-\text{OSolv}} + A_2/\epsilon_2 + 2(A_3/\epsilon_3)]$ is proportional to the original number of moles of substrate. Values of A_3/ϵ_3 for the dimeric product have been multiplied by two in order to account for the fact that 2 mol of substrate are consumed for each mole of dimeric product **3** formed.

$$f_p = \frac{A_p/\epsilon_p}{A_{1-\text{OSolv}}/\epsilon_{1-\text{OSolv}} + A_2/\epsilon_2 + 2(A_3/\epsilon_3)} \quad (1)$$

$$f_3 = \frac{2(A_3/\epsilon_3)}{A_{1-\text{OSolv}}/\epsilon_{1-\text{OSolv}} + A_2/\epsilon_2 + 2(A_3/\epsilon_3)} \quad (2)$$

In one experiment, the time course for the reaction of **1-O₂CC₆H₄-4-NO₂** in 50:50 (v/v) trifluoroethanol–water ($I = 0.50$, NaClO₄) was monitored. The fractional yields of products during this reaction were calculated using Eqns 1 and 2, where the term in the numerator refers to the area of the product peak observed for analysis of a fixed volume of the reaction mixture at a given reaction time, and the terms in the denominator refer to the areas of these product peaks observed after more than 10 reaction half-times. These experiments were conducted using 9-hydroxy-9-methylfluorene as a stable internal standard in order to correct for small variations in the injection volume for different HPLC analyses.

RESULTS

Five products were observed for the solvolysis of **1-O₂CC₆F₅** in 50:50 (v/v) trifluoroethanol–water

Table 1. Yield of the products of reaction of **1-O₂CAr** observed in different solvents^a

Substrate and reaction conditions	Product yield (%) ^b		
	1-OSolv	2	3
1-O₂CC₆F₅ in 50:50 (v/v) methanol–water ^c	98		
	(1-OMe) 30	<1	2
	(1-OH) 68		
1-O₂CC₆F₅ in 50:50 (v/v) trifluoroethanol–water	27		
	(1-OTFE) 3	3	69
	(1-OH) 25		
1-O₂CC₆H₄-4-NO₂ in 50:50 (v/v) trifluoroethanol–water	27		
	(1-OTFE) 3	3	71
	(1-OH) 24		
1-O₂CC₆F₅ in HFIP ^d	<1	100	<1

^a At room temperature ($22 \pm 2^\circ\text{C}$) and $I = 0.50$ (NaClO₄), unless noted otherwise.

^b Product yields were determined by HPLC analysis.

^c Data from Ref. 2.

^d For reaction in a solution of neat HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) which contains no added salt.

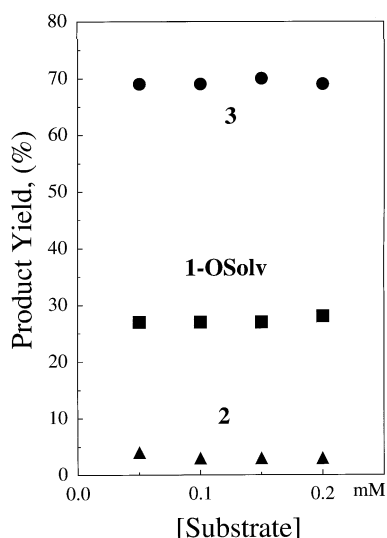


Figure 1. Dependence of the yields of the products of reaction of **1-O₂CC₆F₅** in 50:50 (v/v) trifluoroethanol–water on the concentration of substrate for a reaction at room temperature ($22 \pm 2^\circ\text{C}$) and $l = 0.50$ (NaClO_4)

($l = 0.50$, NaClO_4): the solvent adducts **1-OH** and **1-OTFE**, the alkene **2**, the dimeric product **3** and an unknown product, whose structure was not determined. The peak area from HPLC analysis at 271 nm for this unknown product accounts for less than 2% of the total peak areas for the other reaction products. It was not possible to calculate an absolute yield for this product, whose structure and extinction coefficients could not be determined. This unknown reaction product was ignored when calculating the absolute yields for the other products [Eqns (1) and (2)], because the sum of the yields of these other products was not significantly different from 100%.

The observed yields of the products of reaction of **1-O₂CC₆F₅** and **1-O₂CC₆H₄-4-NO₂** in several different solvents are given in Table 1. The yields reported in Table 1 for reaction in 50:50 (v/v) trifluoroethanol–water should replace the values from an earlier report (42%, **1-OSolv**; 5%, **2**; 53%, **3**),² which were calculated as the simple ratios of the moles of individual product formed divided by the sum of the moles of all reaction products. The earlier calculations of fractional product yields are incorrect because they failed to take into account that 2 mol of substrate are required to form 1 mol of the dimeric product **3** [see Eqns (1) and (2) in the Experimental section].

Figure 1 shows the effect of a fourfold increase in the concentration of **1-O₂CC₆F₅** on the yield of products of solvolysis in 50:50 (v/v) trifluoroethanol–water ($l = 0.50$, NaClO_4).

Figure 2 shows the time course for formation of the products of the reaction of 1×10^{-4} M **1-O₂CC₆H₄-4-NO₂** in 50:50 (v/v) trifluoroethanol–water ($l = 0.50$, NaClO_4).

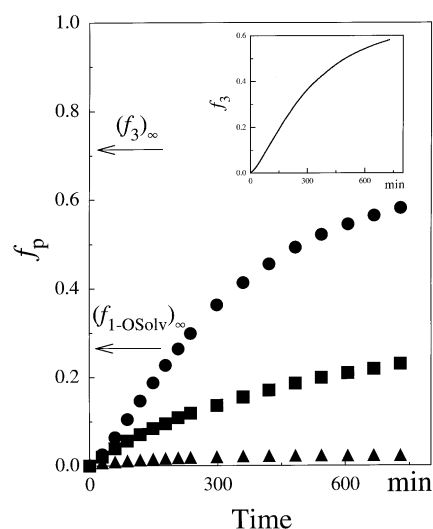


Figure 2. Time course for reaction of **1-O₂CC₆H₄-4-NO₂** (1×10^{-4} M) in 50:50 (v/v) trifluoroethanol–water at 25°C ($l = 0.50$, NaClO_4). The product yields, f_p , are equal to the molar fraction of the original substrate (1×10^{-4} M **1-O₂CC₆H₄-4-NO₂**) consumed in the formation of the product. The final yields of **1-OSolv** and **3** are indicated on the ordinate. (■) **1-OSolv**; (▲) **2**; (●) **3**. The inset omits the experimental points from the time course for formation of the dimeric product **3** in order to show more clearly the lag in the formation of this product

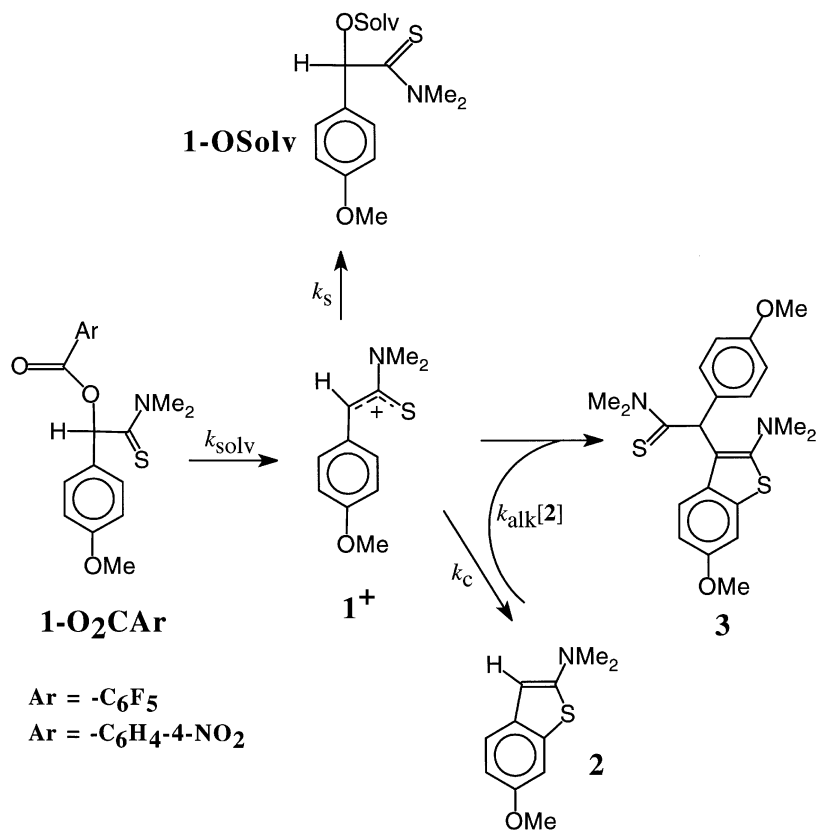
DISCUSSION

It was shown in earlier work that (1) the solvolysis of **1-O₂CAR** in aqueous solvents occurs by a stepwise mechanism through the α -thioamide-stabilized carbocation intermediate **1⁺**;¹ (2) this carbocation intermediate shows a very large selectivity for reaction with azide ion;¹ (3) dimeric **3** is a major product of the reaction of **1-O₂CC₆F₅** in 50:50 (v/v) trifluoroethanol–water;² and (4) the dimeric product **3** forms by nucleophilic addition of **2** to **1⁺** (Scheme 1).²

Rate-determining and product-determining steps for reaction of **1-O₂CAR**

Figure 1 shows that the yields of the products of the reaction of **1-O₂CC₆F₅** in 50:50 (v/v) trifluoroethanol–water, including the dimer, are independent of the concentration of substrate. This observation requires that these products form by reactions that are first-order in the concentration of **1-O₂CC₆F₅**, and is consistent with the conclusion that the rate-determining step for all of these reaction pathways is ionization of the substrate to form **1⁺** and the product-determining step is the partitioning of **1⁺**.

The observed first-order rate constant for solvolysis of **1-O₂CC₆F₅** ($k_{\text{solv}} = 4.2 \times 10^{-3} \text{ s}^{-1}$) is 110-fold larger than for solvolysis of **1-O₂CC₆H₄-4-NO₂** ($k_{\text{solv}} = 3.6 \times 10^{-5}$) in 50:50 (v/v) trifluoroethanol–water,¹ which



Scheme 1

corresponds to a 110-fold faster rate of formation of the carbocation reaction intermediate. This requires the accumulation of a 150-fold larger concentration of the intermediate **1⁺** at the steady state during reaction of **1-O₂CC₆F₅** compared with **1-O₂CC₆H₄-4-NO₂**, because the rate constants for the disappearance of **1⁺** generated by the ionization of these two substrates are the same. Once again, the yield of products of the reaction of **1⁺** are seen to be independent of the steady-state concentration of this carbocation during solvolysis of **1-O₂CAr** (Table 1). The observation of identical yields of products from reaction of **1-O₂CC₆F₅** and **1-O₂CC₆H₄-4-NO₂** requires similar relative *velocities* for partitioning of **1⁺** ($v = k_{alk}[1^+][2]$, $v = k_s[1^+]$ and $v = k_c[1^+]$, Scheme 1) so that the concentration of alkene **2** must be the same during the course of reaction of these two substrates.

The following expression can be derived by making the steady-state assumption for the concentration of the carbocation intermediate **1⁺** ($[1^+]_{ss}$) during the initial stages of the reaction of **1-O₂CC₆H₄-4-NO₂** in 50:50 (v/v) trifluoroethanol–water: $[1^+]_{ss} = (3.6 \times 10^{-5} \text{ s}^{-1}) / (1 \times 10^{-4} \text{ M}) / (k_s + k_c)$, where $k_{solv} = 3.6 \times 10^{-5} \text{ s}^{-1}$ is the observed first-order rate constant for solvolysis of **1-O₂CC₆H₄-4-NO₂** and $1 \times 10^{-4} \text{ M}$ is the initial concentration of the substrate.¹ It is known¹ that $k_s \gg 1 \text{ s}^{-1}$, so that the concentration of the species undergoing dimerization, $[1^+]_{ss}$, is much less than 36 nM. The obser-

vation of dimerization of this dilute electrophilic reagent in a nucleophilic solvent seems, at first glance, incredible. However, dimerization of **1⁺** can be shown to be a logical consequence of the unique chemical reactivity of this compound (Scheme 1).

Reaction mechanism

We were at first confused by the observations that formation of the dimeric product **3** is first order in the concentration of **1-O₂CAr**, and that the yield of this product is independent of the concentration of the steady-state reaction intermediate **1⁺**, because it was expected that the dependence of the yields of the products of simple nucleophilic substitution at **1-O₂CAr** on substrate concentration would be different from that for the formation of a dimeric product. However, these results can be simply explained provided that k_c is the product-determining step for dimerization, so that essentially every mole of **2** formed by cyclization reacts with **1⁺** to form dimer, that is, if **2** does not accumulate to a large extent during the reaction but instead reacts nearly quantitatively with **1⁺** to form dimeric product **3**. With this constraint, the alkene **2** becomes a steady-state reaction intermediate with equal rates of formation by cyclization of **1⁺** and disappearance by nucleophilic addition to **1⁺** to

form **3**. The following experimental observations can be accounted for by treatment of **2** as a steady-state reaction intermediate:

- Figure 2 shows that there is a lag in the formation of the dimeric product **3** at relatively early times during the reaction of **1-O₂CC₆H₄-4-NO₂** while the concentration of **2** increases to a roughly constant *steady-state* concentration.
- The expression for the rate constant ratio for partitioning of the carbocation intermediate **1⁺** between addition of solvent and **2** [eqn (3)] was derived by making the assumption that the concentration of **2** remains constant with time ($d[2]_{ss}/dt = 0 = k_c[1^+] - k_{alk}[1^+][2]_{ss}$) and then solving for $[2]_{ss}$ [Eqn (4)]. This equation predicts that the relative yields of dimeric product **3** and the solvent adducts will depend only upon the rate constant ratio for the partitioning of **1⁺** between nucleophilic addition of solvent (k_s) and intramolecular cyclization to form **2** (k_c). This provides a simple rationalization for the observation of identical product yields from partitioning of the common intermediate of reaction of **1-O₂CC₆F₅** and **1-O₂CC₆H₄-4-NO₂**.

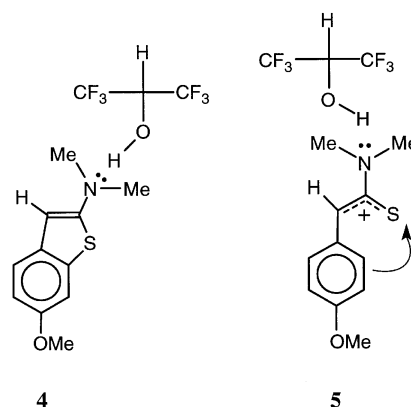
$$\frac{[1 - \text{OSolv}]}{[3]} = \frac{k_s}{k_{alk}[2]_{ss}} = \frac{k_s}{k_c} = 0.8 \quad (3)$$

$$[2]_{ss} = \frac{k_c}{k_{alk}} = 2.3 \times 10^{-6} \text{ M} \quad (4)$$

- Equation (4), which follows directly from the assumption of a constant steady-state concentration for **2**, requires that the concentration of the alkene **2** at the steady state be equal to the rate constant ratio for partitioning of **2** between intramolecular cyclization and reaction with solvent. The concentration of **2** at the steady state is approximately equal to $[2]_{ss} = [1\text{-O}_2\text{CC}_6\text{H}_4\text{-4-NO}_2] f_p = (1 \times 10^{-4} \text{ M}) (0.023) = 2.3 \times 10^{-6} \text{ M}$, where $f_p = 0.023$ is an approximate average fractional conversion of substrate to **2** (Fig. 2). The rate constant ratio $k_{alk}/k_s = 540\,000 \text{ M}^{-1}$ for partitioning of **1⁺** between nucleophilic addition of 50:50 (v/v) trifluoroethanol–water and **2** can then be obtained from Eqn (5), which is derived by combination of Eqns (3) and (4). This value is significantly larger than $k_{alk}/k_s = 70\,000 \text{ M}^{-1}$ determined from the product yields for reaction of **1-O₂CC₆F₅** in the presence of added **2** in 50:50 (v/v) methanol–water.² The difference in these rate constant ratios is primarily the result of the larger nucleophilicity of aqueous methanol compared with aqueous trifluoroethanol.^{2,3} To the best of our knowledge, this is the highest observed nucleophilic reactivity for an alkene compared with the nucleophilic solvent water.^{5,6}

$$\frac{k_{alk}}{k_s} = \frac{[3]}{[2]_{ss}[1 - \text{OSolv}]} = 540\,000 \text{ M}^{-1} \quad (5)$$

Table 1 shows the curious result that a substantial yield of the dimeric product **3** is observed for the reaction of **1-O₂CAr** in 50:50 (v/v) trifluoroethanol–water, but that little or no **3** is observed for the reaction in 50:50 (v/v) methanol–water, a solvent significantly more nucleophilic than aqueous trifluoroethanol, or for the reaction in HFIP, which is much less nucleophilic than aqueous trifluoroethanol.^{7,8} These data show that stringent conditions must be met in order to observe the formation of **3**. Dimerization is unimportant in 50:50 (v/v) methanol–water because the intramolecular cyclization reaction is unimportant in this strongly nucleophilic solvent ($k_s \gg k_c$). The observation that dimerization is also unimportant in HFIP shows that the change from trifluoroethanol–water to this weakly nucleophilic but strongly acidic solvent results in a large increase in k_c compared with k_{alk} . The change probably reflects the opposite effects of hydrogen bonds between solvent and the dimethylamino group on the nucleophilic reactivity of **2** (decrease in k_{alk} , see **4**), and the electrophilic reactivity of the sulfur cation towards addition of the 4-methoxyphenyl ring (increase in k_c , see **5**).



The value of $k_s/k_c = 0.8$ [Eqn (3)] for partitioning of **1⁺** shows that the reactivity of 50:50 (v/v) trifluoroethanol–water in a bimolecular nucleophilic addition reaction is approximately equal to the electrophilic reactivity of the -thioamide group in an intramolecular reaction. This probably represents a large effective molarity⁹ of this functional group in an intramolecular reaction since we are not aware of any reports of bimolecular electrophilic addition of α -thioamide-substituted carbocations to a phenyl ring.

In summary, the dimerization of **1⁺** is the result of (1) the approximately equal rates of cyclization of **1⁺** and nucleophilic addition of 50:50 (v/v) trifluoroethanol–water to **1⁺** ($k_s/k_c = 0.8$, Scheme 1), (2) the large change in the polarity of the benzylic carbon of **1⁺**, from electrophilic to nucleophilic, which occurs on cyclization of **1⁺** to form the carbon nucleophile **2**, and (3) the 5×10^5 times greater reactivity of **2** than the solvent of

50:50 (v/v) trifluoroethanol–water towards addition to $\mathbf{1}^+$ which results in the nearly quantitative addition of $\mathbf{2}$ to $\mathbf{1}^+$ to form $\mathbf{3}$. We view the circumstances here to be so improbable that the dimerization of low concentrations of the steady-state reaction intermediate $\mathbf{1}^+$ will probably remain a completely unique organic reaction.

Acknowledgment

This work was supported by grant GM 39754 from the National Institutes of Health.

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