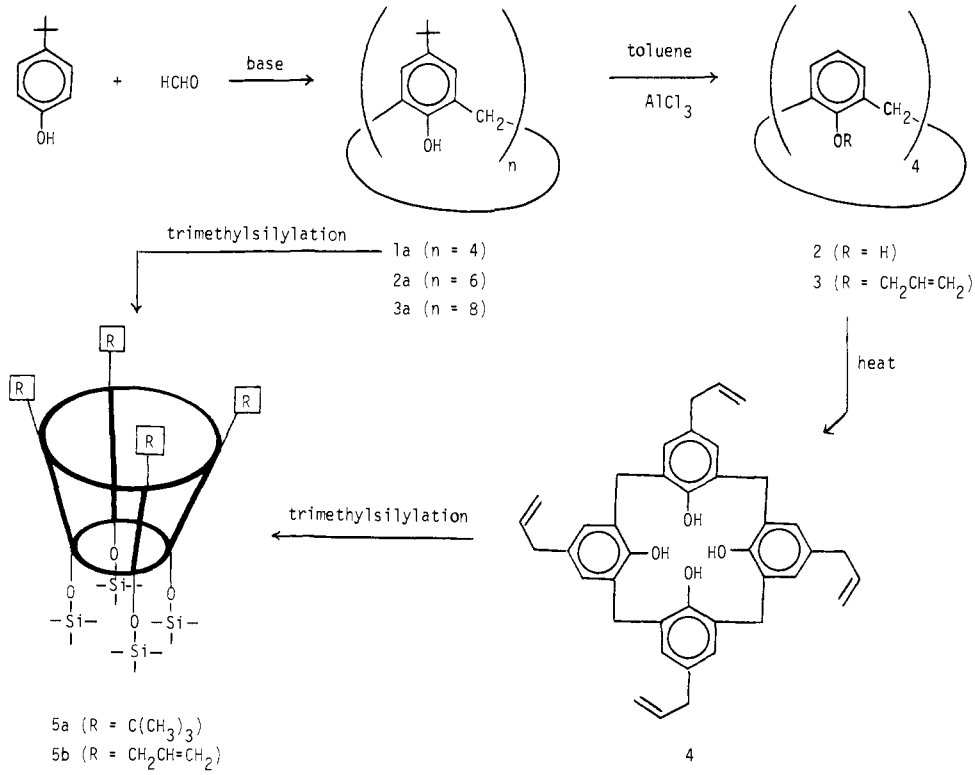
Scheme I



conformation is a downfield singlet for the aryl hydrogens, a pair of doublets at midfield for the methylene hydrogens, and two upfield singlets from the *tert*-butyl and trimethylsilyl hydrogens, respectively. We have prepared compound **5a** by the action of *N,O*-bis(trimethylsilyl)acetamide[15] on **1a** in CH_3CN solution. After being heated for 16 h in an atmosphere of N_2, it was obtained in 92% yield as colorless, long blades: mp 338 °C (softening at 315–320 °C); ^1H NMR (Me_4Si, $CDCl_3$) δ 6.76 (s, 8, ArH), 4.37 (d, 4, J = 12 Hz, CH_2), 2.97 (d, 4, J = 12 Hz, CH_2), 1.00 (s, 36, $C(CH_3)_3$), 0.26 (s, 36, $Si(CH_3)_3$). Anal. Calcd for $C_{56}H_{88}O_4Si_4$: C, 71.79, H, 9.40. Found: C, 71.51; H, 9.47. The ^1H NMR of **5a** accords exactly with that predicted for a "cone" conformation, indicating that it is a conformationally rigid molecule possessing what has been called an "enforced cavity".[16] In comparable fashion, **4** was converted to the tetrakis(trimethylsilyl) ether (**5b**) and obtained as colorless, fine needles: mp 173–181 °C; ^1H NMR (Me_4Si, $CDCl_3$) δ, 6.43 (s, 8, ArH), 6.03–5.43 (m, 4, vinyl H), 5.13 (br s, 4, vinyl H), 4.93–4.63 (m, 4, vinyl H), 4.31 (d, 4, J = 12 Hz, $ArCH_2Ar$), 3.12 (br, s, 8, $CH_2CH{=}CH_2$), 3.02 (d, 4, J = 12 Hz, $ArCH_2Ar$), 0.26 (s, 36, $Si(CH_3)_3$). Anal. Calcd for $C_{52}H_{72}O_4Si_4$: C, 71.50; H, 8.31. Found: C, 71.49; H, 8.45. The downfield singlet for the aryl hydrogens and the upfield singlet for the trimethylsilyl hydrogens are both in complete accord with the "cone" conformation. Although the resonances from the methylene hydrogens of the allyl groups overlay some of those arising from the $ArCH_2Ar$ methylene hydrogens, the downfield doublet arising from the latter is cleanly displayed at δ 4.38 and the upfield doublet is clearly discernible in the pattern near δ 3.0.

Compound **5b** represents what may be the closest current approach to a *synthetic* molecule that has an architecture comparable to that of the cyclodextrins. Since *p-tert*-butylcalix[6]arene and *p-tert*-butylcalix[8]arene are also readily available starting materials and since the allyl group is amenable to conversion to a variety of functional groups, this synthetic approach has the promise of providing a variegated collection of molecules with large cavities.

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Registry No. 1a, 60705-62-6; **2**, 74568-07-3; **3**, 81294-22-6; **4**, 81294-23-7; **5a**, 81294-24-8; **5b**, 81315-60-8; *p*-(*tert*-butyl)phenol, 98-54-4; formaldehyde, 50-00-0.

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Abnormally High Nucleophilicity of Micellar-Bound Azide Ion

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Rate enhancements of bimolecular reactions in aqueous micelles are typically caused by concentration of both reactants into the small volume of the micellar pseudophase. For both nonfunctional and functional micelles, second-order rate constants in the micellar pseudophase are similar to or smaller than those in water.[2-11]

(1) Department of Physical Chemistry, Faculty of Sciences, University of Alcala de Henares, Madrid, Spain.
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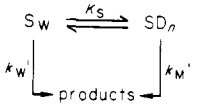
Table I. Second-Order Rate Constants in Aqueous and Micellar Pseudophase[a]

substrate	medium				
	H_2O	CTABr	CTACl	CTAOMes	$CTAN_3$
DNCB[b]	4.6×10^{-5}	2.4×10^{-3}	2.4×10^{-3}		1.3×10^{-3}
DNCN[c]	0.001	0.4	0.4		~0.2
$PhCO{\cdot}OC_6H_3(NO_2)_2$[d]	0.24	0.24			
$PhSO_3Me$[e]	3.5×10^{-4}			2.5×10^{-4}	1.5×10^{-4}

[a] Values of k_W and k_2^m, M^{-1} s^{-1}, in aqueous and micellar pseudophase respectively at 25.0 °C; k_2^m is based on $K_{Br}^{N_3} = 2$, $K_{Cl}^{N_3} = 1.3$, $K_{OMes}^{N_3} = 1.1$, and $\beta = 0.7$–0.8.[2,4-6,8] [b] $K_S = 67$, 82, and 115 M^{-1} in CTABr, CTACl, and $CTAN_3$, respectively. [c] $K_S = 600$ M^{-1} in both CTABr and CTACl and >600 M^{-1} in $CTAN_3$. [d] $K_S = 650$ M^{-1} in CTABr. [e] $K_S = 55$ and 70 M^{-1} in CTAOMes and $CTAN_3$, respectively.

Scheme I



Nucleophilic aromatic substitution by azide ion is an unexpected exception to this generalization, and second-order rate constants of reaction with 2,4-dinitrochlorobenzene and naphthalene (DNCB and DNCN) are much larger in the micellar pseudophase than in water.

The kinetic analysis follows Scheme I,[12] where S is the substrate, D_n is the micellized surfactant, K_S is the binding constant of S to the micelles, written in terms of micellized surfactant,[13] and k_W' and k_M' are *first-order* rate constants in aqueous and micellar pseudophase, respectively, given by[5,11]

$$k_W' = k_W[N_{3W}^-] \quad (1)$$

$$k_M' = k_M m_{N_3}^s = k_M[N_{3M}^-]/[D_n] \quad (2)$$

In eq 1 and 2 k_W and k_M are second-order rate constants, but k_M is defined in terms of the mole ratio of bound N_3^- to micellized surfactant.[5,11] The equations give eq 3 for the first-order rate

$$k_\psi = (k_W[N_{3W}^-] + k_M K_S[N_{3M}^-])/(1 + K_S[D_n]) \quad (3)$$

constant k_ψ.[5] (The quantities in squared brackets are molarities in terms of solution volume.)

For mixtures of NaN_3 and CTAX we write the distribution of N_3^- between water and micelles in terms of eq 4.[2,4-6]

$$K_X^{N_3} = [N_{3W}^-][X_M^-]/([N_{3M}^-][X_W^-]) \quad (4)$$

The parameters in eq 3 and 4 can be estimated by fitting experimental rate-constant–surfactant profiles to these equations (Figure 1).[11,14] The rate constants k_M and k_W have different dimensions, but we convert k_M, s^{-1}, into k_2^m, M^{-1} s^{-1}, assuming that reaction occurs in the micellar Stern layer whose molar volume is 0.14 L, so that[16,17]

$$k_2^m = 0.14 k_M \quad (5)$$

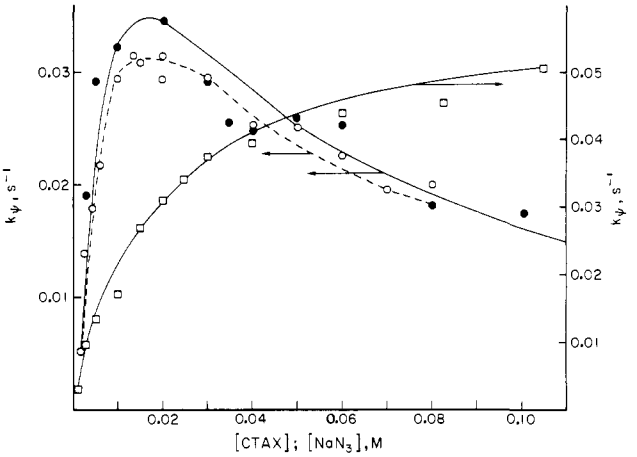


Figure 1. Reaction of N_3^- with 2,4-dinitrochlorobenzene in CTACl with 0.01 M NaN_3, (●) in CTABr with 0.01 M NaN_3 (○) in 0.015 M CTABr and variable NaN_3 (□). The lines are calculated from the parameters in Table I.

Figure 1 illustrates the fit of experimental and calculated data for some reactions of DNCB, and the second-order rate constants, k_2^m, are in Table I. The kinetically estimated values of K_s for DNCB and DNCN are consistent with literature values.[3,16b,18a]

Some reactions were also followed in cetyltrimethylammonium azide ($CTAN_3$) in the absence of inert counterions and, therefore, with no ionic competition for the cationic micelles.[18,19] Under these conditions k_ψ increases steadily to a constant value as substrate becomes fully micellar bound, and the values of k_2^m calculated from these experiments[18] are similar to those in mixtures of NaN_3 and CTAX (Table I). The (small) differences between k_2^m in different surfactants are probably due to our assuming the same volume element of reaction for each surfactant.

For reactions of DNCB and DNCN with N_3^-, $k_2^m \gg k_W$. We know of no other bimolecular reactions in aqueous micelles that behave in this way,[2-11,16,18] and the micelles are affecting the free energy of the transition state relative to the initial state.[20] However, for reactions of N_3^- with 2,4-dinitrophenyl benzoate or methyl benzenesulfonate,[21] $k_2^m \approx k_W$ (Table I), and the rate enhancements are accounted for by concentration of the reactants into the micellar Stern layer so that micellar effects upon aromatic substitution by N_3^- represent a special case.

The structure of N_3^- is different from that of most anions in that the resonance description involves one nitrogen carrying a double negative charge in one canonical form.[22]

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(13) The concentration of monomeric surfactant is assumed to be given by the critical micelle concentration (cmc)[12] so that for cetyltrimethylammonium surfactant, CTAX (X = Cl, Br, OMes), $[D_n]$ = [CTAX] − cmc.
(14) At 25.0 °C $k_W = 4.6 \times 10^{-5}$ M^{-1} s^{-1} for reaction of DNCB + NaN_3, in reasonable agreement with the value of 3×10^{-5} M^{-1} s^{-1} estimated from data at higher temperatures.[15]
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(17) Taking the volume element of reaction as that of the whole micelle[6-8,10] gives $k_2^m \approx 0.35 k_M$, i.e., approximately double the values quoted in Table I.
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(19) The surfactant was made from $(CTA)_2SO_4$ and $Ba(N_3)_2$ in CO_2-free water, and removal of $BaSO_4$ follows the method used for preparation of CTAOH.[18c]
(20) Such relative free-energy differences are responsible for micellar rate effects upon unimolecular reactions.[5]
(21) Halide ion surfactants could not be used with this substrate because of the nucleophilicity of the halide ions.

$$^{-}N{=}N^{+}{=}N^{-} \leftrightarrow N{\equiv}N^{+}{-}N^{2-}$$

This charge distribution is probably responsible for the high nucleophilicity of N_3^- toward carbocations, as given, for example, by the N^+ scale,[23] and polarization of N_3^- by a strong electrophile could be responsible for this high reactivity, so that cationic micelles could have the same effect. However the rate effects in deacylation or S_N2 displacement (Table I) suggest that the micelle is stabilizing the transition state for aromatic nucleophilic substitution but not for the other reactions.

In the absence of micelles N_3^- is unusually unreactive in aromatic nucleophilic substitution, based on the N^+ scale,[15] so it seems that unfavorable transition-state interactions disappear in a reaction in a cationic micelle as compared with reaction in water or alcoholic solvent.

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(Glutathiomethyl)glyoxal: Mirror-Image Catalysis by Glyoxalase I

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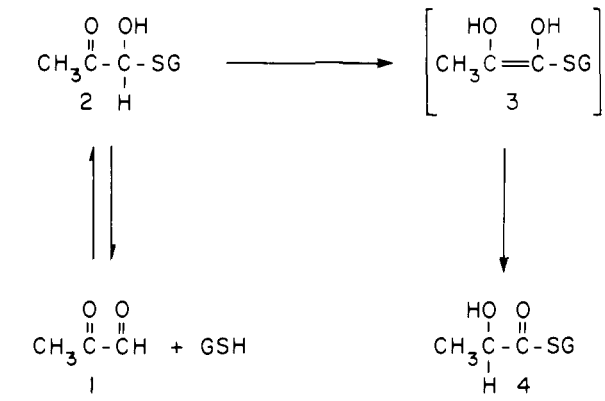
Glyoxalase I [*S*-lactoylglutathione methylglyoxal-lyase (isomerizing) EC 4.4.1.5; GX I] catalyzes the conversion of the thiohemiacetal **2** of α-keto aldehyde **1** and glutathione [*N*-(*N*-L-γ-glutamyl-L-cysteinyl)glycine; GSH] to the thioester **4** of an α-hydroxy acid and GSH (Scheme I).[1] The reaction proceeds via a fast-shielded proton transfer with the intermediacy of enediol **3**,[2] and the resulting acid has been established as the D isomer.[3] Recent ^1H NMR studies have suggested that one of the two diastereomeric thiohemiacetals is selectively processed.[4] Two general observations concerning the substrate specificity of the enzyme have been made. First, the specificity for GSH is high; aside from *N*-acyl derivatives of GSH and several related tripeptides, other sulfhydryl-containing compounds are inactive primarily due to poor binding.[5] Second, the specificity for α-keto aldehydes is broad, indicating a high tolerance at that region of the active site.[1,2,3b,6] During our study of β-(alkylthio)-α-keto aldehydes, **6**, we found that one member of this class, (glutathiomethyl)glyoxal (**6a**),[7] exhibits two surprising properties in its reaction with glyoxalase I: *a loss of glutathione specificity for thioester formation and the production of the* L *isomer of the resulting α-hydroxy acid.* We believe that these findings are only

Scheme I



Scheme II

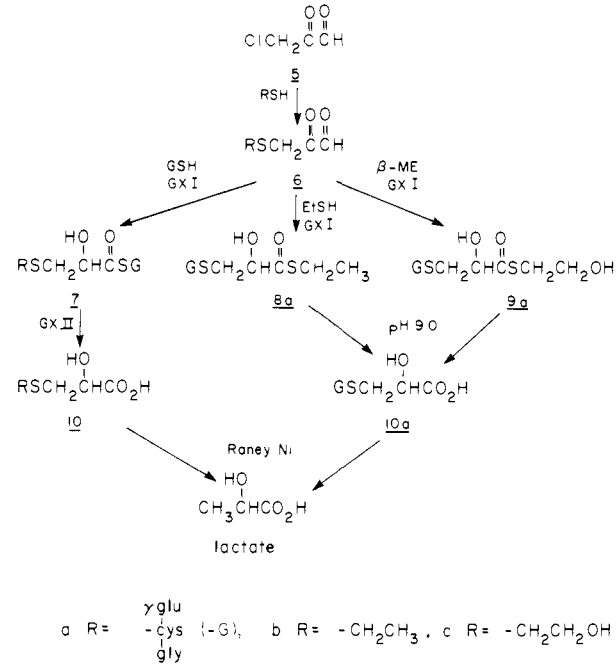


Table I. Relative Velocities of the Reaction of [(Alkylthio)methyl]glyoxals and Thiols with Glyoxalase I and of the Hydrolysis of the Thioesters by Glyoxalase II

substrate	thiol	rel velocity GX I[a]	rel velocity GX II
6a	GSH	83	100
	EtSH	40	0.4
	β-ME	25	0
6b	GSH	100	100
	EtSH	0	
	β-ME	0	
6c	GSH	73	70
	EtSH	0	
	β-ME	0	

[a] Measured spectrophotometrically. Under identical conditions, methylglyoxal gives a relative velocity of 134 (2.5 μmol/min) with GSH and is inactive with EtSH and β-ME.

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(7) The proper (current Chemical Abstracts Index) name for **6a** is *N*-[*N*-L-γ-glutamyl-*S*-(2,3-dioxopropyl)-L-cysteinyl]glycine. We propose the trivial name (glutathiomethyl)glyoxal to reflect the homology with other β-(alkylthio)-α-keto aldehydes.

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