Micellar Catalysis of Organic Reactions. 25. Orientational Effects in Hydroxy-Functionalized Micelles†

Trevor J. Broxton,* John R. Christie, and Xenia Sango

Department of Chemistry, La Trobe University, Bundoora, Victoria, Australia 3083

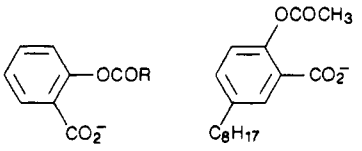
Received September 8, 1988

The basic hydrolysis of a number of aspirin derivatives in the presence of the hydroxy-functionalized micelles cetyl(2-hydroxyethyl)dimethylammonium bromide (CHEDAB), cetyl(2-hydroxypropyl)dimethylammonium bromide (CHPDAB), and (2-hydroxycetyl)trimethylammonium bromide (2-OH CTAB) and in the presence of cetyltrimethylammonium bromide (CTAB) has been compared. It has been found that of the hydroxy-functionalized micelles CHEDAB best discriminates between substrates with reaction centers at the micelle–water interface and those with reaction centers that are more deeply buried in the micellar interior. This discrimination is shown in differences in the ratios of the optimum rates of hydrolysis in the hydroxy-functionalized micelles and in CTAB. It is also shown in the ratios of the calculated rates of reaction in the micellar pseudophase for the hydroxy-functionalized micelles and for CTAB. Thus the orientation of substrates within micellar aggregates is important in determining the magnitude of micellar catalysis.

Introduction

The orientation of substrates solubilized by micelles and the consequences of this orientation on the magnitude of micellar catalysis are currently of interest.[1-3] Conflicting reports concerning the dependence of the magnitude of micellar catalysis on substrate orientation exist. In general, two approaches have been used to influence the substrate orientation within micelles. Firstly, hydrophobic alkyl groups in the substrate have been assumed to be anchored in the hydrophobic core of the micelle. Secondly, substrates containing anionic groups such as the carboxylate group, CO_2^-, have been used, and it has been assumed that these ionic groups would preferentially be found protruding from the micelle surface into the aqueous intermicellar pseudophase. These influences have been assumed to orient the reaction center of substrates in predictable ways. Few of these studies have been supported by spectroscopic studies to confirm the actual orientation of the substrate in the micelle. Recent reports of the orientation of salicylate ions[4,5] in micelles on the basis of NMR studies in D_2O and in cetyltrimethylammonium bromide (CTAB) have led to some studies of substrate orientation in micelles.[1,3]

The study of aspirin derivatives 1–3 makes use of both approaches described above to influence substrate orientation in micelles.[3]



1: R = CH_3
2: R = C_7H_{15}

3

As a result of NMR and viscoelasticity studies, it has been concluded[3] that for compounds 1 and 3 the reaction center is either at the interface or in the aqueous intermicellar pseudophase, while for compound 2 the reaction center is pulled further into the micelle.

These differences in orientation are manifested in the activation parameters for intramolecular general base-catalyzed hydrolysis at pH 7. In strongly basic solution,[3] they are manifested in the magnitude of the ratio of the second-order rate constants for reaction in the micellar pseudophase and in aqueous solution (i.e., k_2^M/k_2^W).

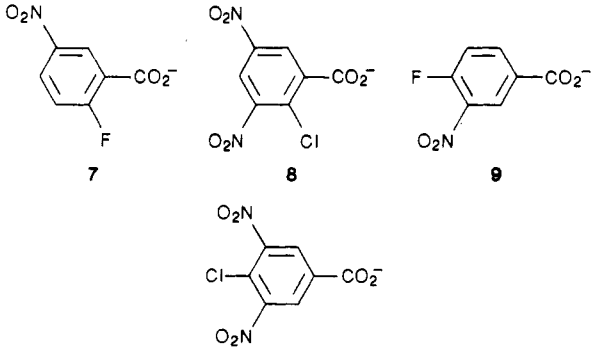
We now report kinetic data for the basic hydrolysis of compounds 1–3 in the presence of hydroxy-functionalized micelles 4–6, and we interpret the observed differences between the hydroxy-functionalized micelles and CTAB in terms of the reported differences in the orientation of compounds 1–3 in micelles.[3] Reaction in the presence of hydroxy-functionalized micelles is of interest because covalent-bond formation between the micellar hydroxyl group and the ester carbonyl group is required.[6]

$C_{16}H_{33}NMe_2{}^+CH_2CH_2OH,Br^-$ (4) (CHEDAB)

$C_{16}H_{33}NMe_2{}^+CH_2CHOHCH_3,Br^-$ (5) (CHPDAB)

$C_{14}H_{29}CHOHCH_2NMe_3{}^+,Br^-$ (6) (2-OH CTAB)

Similarly, the magnitude of k_2^M/k_2^W for hydroxydehalogenation of some halonitrobenzoate substrates (7–10) was found to be larger for substrates with the CO_2^- group ortho to the reaction center and hence with the reaction center at the micelle–water interface (7, 8) than for those with the CO_2^- group para to the reaction center and hence with the reaction center more deeply buried into the interior of the micelle (9, 10).[1]



7 8 9

10

Substrate orientations for substrates 7–10 were determined by NMR measurements, and conclusions were in accord with the ionic carboxylate group being present at the micelle–water interface.

† Part 24: Broxton, T. J.; Christie, J. R.; Chung, R. P.-T. *J. Phys. Org. Chem.*, in press.

(1) Broxton, T. J.; Christie, J. R.; Chung, R. P.-T. *J. Org. Chem.* **1988**, *53*, 3081.
(2) Witte, F. M.; Engberts, J. B. F. N. *J. Org. Chem.* **1985**, *50*, 4130.
(3) Broxton, T. J.; Christie, J. R.; Sango, X. *J. Org. Chem.* **1987**, *52*, 4814.
(4) Manohar, C.; Rao, U. R. K.; Valaulikar, B. S.; Iyer, R. M. *J. Chem. Soc., Chem. Commun.* **1986**, 379.
(5) Rao, U. R. K.; Manohar, C.; Valaulikar, B. S.; Iyer, R. M. *J. Phys. Chem.* **1987**, *91*, 3286.
(6) Martinek, K.; Levashov, A. V.; Berezin, I. V. *Tetrahedron Lett.* **1975**, 1275.

0022-3263/89/1954-1919$01.50/0

On the other hand, no significant differences in k_2^M/k_2^W were found[2] for the hydrolysis of a series of sulfonylmethyl sulfonate esters (11) of widely varying hydrophobicity in the terminal alkyl groups R_1 and R_2.

$$R_1SO_2CH_2OSO_2R_2$$
11

For these compounds, varying the hydrophobicity of either R_1 or R_2 had no effect on the magnitude of k_2^M/k_2^W, and it was concluded by Engberts that in this case the substrate was bound to the micelle surface rather than taken into the micelle.[2] It seems to us that this may be a reflection of the presence of polar groups in the middle of the molecule and hydrophobic groups at each end resulting in an orientation with the hydrophobic groups in hydrophobic binding sites at the surface of the micelle rather than in the micellar core because of the requirement that the polar groups are in a polar region at the interface. Thus the polar groups in the middle of substrate 11 tend to pull the rest of the molecule out of the micellar core.

Furthermore, a computer program has been used to simulate the variation of the observed rate as a function of detergent concentration, in an effort to determine the rate constant for reaction within the micellar pseudophase (k_2^M), the binding constant of the substrate to the micelle (K_s), and the exchange constant for the micellar counterion and the reactive nucleophile (K_{Br}^{Nuc}. This program was developed previously[3,7] for use with CTAB, but it has been used here for reactions in the hydroxy-functionalized micelles **4–6**. Since the extent of ionization of hydroxy-functionalized micelles varies with hydroxide concentration, a constant hydroxide concentration was used throughout this work to maintain a constant percentage of ionization of the hydroxy groups of the micelle.

On the face of it, the reaction scheme here is considerably more complex than that in CTAB micelles, but a careful consideration of the system leads to considerable simplification. There are three distinct micellar reactions that can lead to the phenolic product and must be considered.

$$OH^-(micelle) + RCOOAr \rightarrow ArOH + RCOO^- \quad (1)$$

$$Mic^+OH(micelle) + RCOOAr \rightarrow ArOH + Mic^+OOCR \quad (2)$$

$$Mic^+O^-(micelle) + RCOOAr \rightarrow ArO^- + Mic^+OOCR \quad (3)$$

There are two justifications for supposing that reaction 1 is unlikely to be important. Firstly, the micellar alkoxide is a weaker base than hydroxide ion (the pK_a for CHEDAB is 12.4), and so one would expect that hydroxide ion would fairly promptly remove a proton from the micellar hydroxyl group on its arrival in the micelle. That is, the concentration of the zwitterionic micellar alkoxide would be at least 20 times that of micellar hydroxide ion. Secondly, it is observed that the production of phenolic species proceeds considerably more rapidly in CHEDAB than in CTAB. Yet the first reaction ought to have a similar rate in the two micellar environments. The fast production of product must therefore be due to another reaction. Reaction 2 can also be considered of minor importance on purely mechanistic grounds. The alkoxide must be a considerably stronger nucleophile than the corresponding alcohol, and so the only way that this reacton could contribute would be if the alcohol concentration swamped that of the alkoxide. There is ample evidence that this cannot be the case in this system at the hydroxide concentration

Table I. Pseudo-First-Order Rate Constants ($10^3 \times k_\psi/s^{-1}$) for the Basic Hydrolysis (0.01 M NaOH) of Aspirin (1) in the Presence of Micelles at 56.4 °C

[detergent], mM	CTAB	CHEDAB	CHPDAB	2-OH CTAB
0	8.23			
1	14.9	158	26.5	15.0
2	27.3	270	47.7	45.2
4	27.6	339	53.6	59.7
8	27.1		46.3	55.6
12	21.5	329	42.0	48.2
16	18.9		37.8	44.9
20		236	33.4	38.0
24	15.1		29.6	35.0
28	14.6	232	26.2	30.0

Table II. Pseudo-First-Order Rate Constants ($10^3 \times k_\psi/s^{-1}$) for the Basic Hydrolysis (0.01 M NaOH) of Compound 2 in the Presence of Micelles at 56.4 °C

[detergent], mM	CTAB	CHEDAB	CHPDAB	2-OH CTAB
0	3.02			
1	5.97	39.0	8.72	11.4
2	6.72	40.3	9.12	13.2
4	6.53	37.7	8.47	12.1
8	4.72		6.68	9.23
12	3.80	27.2	5.32	7.69
16	3.50		4.73	6.70
20	3.11	21.9	3.95	5.90
24	2.79		3.31	5.26
28	2.52	7.27	3.06	4.50

used. Thus we need only consider reaction 3, together with the distribution

$$OH^-(W) + Mic^+OH,Br^-(M) \rightarrow Mic^+O^-(M) + H_2O + Br^-(W)$$

and direct hydrolysis of the substrate by hydroxide ion in the aqueous pseudophase.

This simplified reaction scheme is directly analogous with that used in the previous studies with CTAB,[1,3] and so the same mathematical treatment will serve, with simple replacement of K_{Br}^{OH} by K_{Br}^{MicO}. In our calculations, we have used 3×10^{-4} M for the cmc of CTAB.[1,3] For CHEDAB, it is reported[8] that the cmc in basic solution (0.1 M NaOH) is 3.5×10^{-5} M, much less than in neutral solution (8×10^{-4} M), presumably because of reduced head-group repulsions in the zwitterion.[8] The cmc values of the three hydroxy-functionalized micelles in neutral solution are reported to be similar,[9] ranging from 0.8 mM for CHEDAB to 1.3 mM for 2-OH CTAB and 1.0 mM for CHPDAB. We have therefore assumed a similar value for the cmc of all the hydroxy-functionalized micelles in basic solution. Any reduction in head-group repulsions for CHEDAB should also be present for CHPDAB and for 2-OH CTAB because of the similar structure of the zwitterions. In each case, the positive and negative charges are separated by two sp^3-hybridized carbons, although the actual geometry in each case may vary slightly.

Results and Discussion

Observed pseudo-first-order rate constants for the basic hydrolysis of compounds **1–3** at 56 °C and pH 12 are in Tables I–III, respectively. In an attempt to determine if any of the hydroxy-functionalized micelles differentiate between reaction centers located at the micelle–water interface (e.g., compounds **1** and **3**) and those more deeply buried inside the micelle (e.g., compound **2**), we first

(7) Broxton, T. J.; Christie, J. R.; Mannas, S. M. *Aust. J. Chem.* **1988**, *41*, 325.

(8) Bunton, C. A.; Paik, C. H. *J. Org. Chem.* **1976**, *41*, 40.
(9) Broxton, T. J.; Chung, R. P.-T. *J. Org. Chem.* **1986**, *51*, 3112.

Table III. Pseudo-First-Order Rate Constants ($10^3 \times k_\psi/s^{-1}$) for the Basic Hydrolysis (0.01 M NaOH) of Compound 3 in the Presence of Micelles at 56.4 °C

[detergent], mM	CTAB	CHEDAB	CHPDAB	2-OH CTAB
0	5.88			
1	37.2		80.0	90.6
2	35.8		77.7	121
4	34.5	498	74.0	109
8	27.1		59.6	71.
12	22.5	403	48.1	65.2
16	20.8		38.1	54.6
20	18.5	347	36.3	47.6
24	16.3		30.9	41.6
28	14.8	290	29.6	34.6

Table IV. Estimated Micellar Parameters for the Basic Hydrolysis (0.01 M NaOH) of Compounds 1–3 at 56.4 °C[a]

	K_s		
	1	2	3
CTAB[b]	360	1715	2085
CHEDAB[c]	215	1181	367
CHPDAB[c]	305	1525	2062
2-OH CTAB[c]	196	1439	1558
	k_2^M		
	1	2	3
CTAB[b]	0.0127	0.0020	0.0115
CHEDAB[c]	0.2610	0.013 71	0.2393
CHPDAB[c]	0.0260	0.002 78	0.0242
2-OH CTAB[c]	0.0303	0.003 82	0.0333

[a] K_s in M^{-1}, k_2^M in $M^{-1}\ s^{-1}$. [b] Using $K_{Br}^{MicO} = 2$; cmc $= 3 \times 10^{-4}$ M; $\beta = 0.8$. [c] Using $K_{Br}^{MicO} = 2$; cmc $= 3.5 \times 10^{-5}$ M; $\beta = 0.8$.

Table V. Ratios of the Maximum Observed Rates ($k^{M\text{-}OH}/k^{CTAB}$) for the Basic Hydrolysis (0.01 M NaOH) of Compounds 1–3 at 56.4 °C in Hydroxy-Functionalized Micelles and in CTAB

	$k^{M\text{-}OH}/k^{CTAB}$		
compound	CHEDAB	CHPDAB	2-OH CTAB
1	12.3	2.30	2.16
2	6.0	1.36	1.96
3	13.4	2.15	3.25

compared the maximum observed rates in each micelle to those in CTAB. These results (Table V) show that CHEDAB (4) strongly differentiates between compounds with reaction centers at the interface (1 and 3) and that with a reaction center more deeply buried into the micelle (2). For compounds 1 and 3, the maximum observed rate in CHEDAB was 12–13 times faster than that in CTAB. However, for compound 2, this ratio was reduced to 6. CHPDAB (5), on the other hand, differentiated only weakly between these substrate orientations, while 2-OH CTAB (6) did not differentiate between these substrate orientations to any significant extent.

Secondly, we compared the ratio of the calculated rate of reaction within the micellar pseudophase (k_2^M) for the hydroxy-functionalized micelles and for reaction in CTAB (Table VI). Once again CHEDAB strongly differentiated between compound 2, with its reaction center buried into the micelle, and compounds 1 and 3, with their reaction centers at the interface, while 2-OH CTAB differentiated only weakly between these differences in substrate orientation and CHPDAB did not differentiate at all.

To rationalize these differences in the ability of different hydroxy-functionalized micelles to discriminate between different substrate orientations, we should consider the structure of micelles 4–6 and the location of the hydroxyl groups within them. For example, in CHEDAB (4), the

Table VI. Ratio of Calculated Rates ($k_2^{M\text{-}OH}/k_2^M$) for the Basic Hydrolysis (0.01 M NaOH) of Compounds 1–3 at 56.4 °C in the Hydroxy-Functionalized Micelles and in CTAB

	$k_2^{M\text{-}OH}/k_2^M$		
compound	CHEDAB	CHPDAB	2-OH CTAB
1	20	2.0	2.3
2	7.1	2.0	1.4
3	20.5	2.9	2.1

Table VII. Ratios of Maximum Observed Rates for CHEDAB and for CTAB at 29.4 °C as a Function of the Hydroxide Concentration for the Basic Hydrolysis of Compounds 1–3

	k^{CHEDAB}/k^{CTAB}		
[NaOH], mM	1	2	3
46.5	6.45	5.7	14.4
9.30	12.8	4.1	26.6
4.65	17.2	9.9	31
0.93	21.2	10.8	28.6

hydroxyl group is mobile and either at the micelle–water interface or protruding into the aqueous intermicellar pseudophase. In CHPDAB (5), however, because of the extra methyl group, it is possible that the hydroxy group is in a slightly more hydrophobic region. For 2-OH CTAB, it is likely that the hydroxyl group is embedded into the micelle surface or even dragged slightly down into the interior of the micelle. It is therefore reasonable that CHEDAB would best differentiate between reaction centers at the micelle surface and those more deeply buried into the micellar interior. It might be expected at first glance that 2-OH CTAB would be the best catalyst for a substrate in which the reaction center is more deeply buried into the micelle. However, we should not forget that the hydroxy group in CHEDAB is primary and therefore more reactive than the secondary hydroxy groups of CHPDAB (5) and 2-OH CTAB (6). This factor overrides orientational effects on the raw rate constants, but we are still left with significant differences between the magnitude of catalysis of CHEDAB and CTAB for compounds 1 and 3 and for compound 2.

The magnitudes of K_s for compounds 1 and 2 are similar in CTAB and in each of the hydroxy-functionalized micelles (Table IV), and since the magnitude of K_s is sensitive to the value of the cmc chosen,[3] this lends support to our assumption that the cmc values of each of the hydroxy-functionalized micelles are similar in basic solution. Furthermore, compounds 2 and 3, which contain hydrophobic alkyl groups, have larger K_s values (Table IV) than compound 1, as expected. The surprisingly low K_s value for compound 3 in CHEDAB is possibly a result of the limited number of data points for this compound in this micelle. Rate constants at lower CHEDAB concentrations would be useful to determine if the rate at 4 mM is a maximum or whether the maximum is at 1 or 2 mM as found in the other micelles, but the very fast rate constants found in this system limit the range of CHEDAB concentrations that could be used for reactions followed by conventional kinetic methods.

It could be argued that the kinetic effects observed for CHEDAB may be due to the greater ionization of this micelle, which contains primary hydroxyl groups, than that of either CHPDAB or 2-OH CTAB, which contain secondary hydroxyl groups. However, it can be seen (Table VII) that the differentiation between substrates 1, 2, and 3 by CHEDAB is present over a range of hydroxide concentrations (0.93–9.30 mM) and thus for systems with varying degrees of ionization of the micellar hydroxyl groups. Of particular interest is the observation that for

aspirin (1) the rate ratio k^{CHEDAB}/k^{CTAB} increases as the hydroxide concentration is reduced. This effect is also present for substrates 2 and 3, but it is more obvious for substrate 1. Thus, at the highest base concentration, where we expect more ionization of the micellar hydroxyl groups to the reactive alkoxide ions, the rate ratio is less than at lower hydroxide concentrations. This effect can be explained by considering the factors leading to incorporation of the substrates into the micelles. Two major effects, electrostatic attraction between the substrate carboxylate groups and the cationic micelles and the hydrophobicity of the substrates, lead to incorporation of the substrates into the micelles. As the hydroxyl groups of the micelles become ionized, the micelle changes from a cationic to a zwitterionic aggregate and the electrostatic attraction between the substrate and micelle is lost. Thus, at the higher base concentrations, the substrates are less efficiently bound to the micelles. This effect is more important for compound 1 than for either of compounds 2 or 3 because both compounds 2 and 3 possess hydrophobic alkyl chains that lead to efficient incorporation into the micelles. Aspirin (1) does not have this additional factor leading to efficient incorporation of the substrate into the micelle.

Experimental Section

Materials. Substrates 1–3 were available from previous work.[3] Hydroxy-functionalized micelles 4–6 were prepared as previously described.[9]

Kinetics. Stock solutions of substrates (0.01 M in dioxane), detergents (0.02 M in water), and sodium hydroxide were prepared. The rate measurements were carried out as described previously.[3,10] Required volumes of micelle and sodium hydroxide solution were mixed and allowed to reach thermal equilibrium in a cuvette (3 mL) contained in the jacketed cell compartment of the UV–vis spectrophotometer. Then a solution of the required substrate in dioxane (18 μL) was added to initiate the reaction, and product formation was followed at 297 nm for compounds 1 and 2 and 303 nm for compound 3. The rate of change of absorbance was followed by means of a National VP6511 X-T recorder, and reactions were followed for 10 half-lives to obtain an experimental infinity value. Rate constants were obtained by a least-squares analysis of the plots of log ($Abs_\infty - Abs_t$) against time. Rate constants presented in Tables I–III were all obtained in duplicate, and the reproducibility in all cases was within ±2%.

Registry No. 1, 50-78-2; 2, 70424-62-3; 3, 95772-48-8; CTAB, 57-09-0; CHEDAB, 20317-32-2; CHPDAB, 68796-83-8; 2-OHCTAB, 102831-87-8.

(10) Broxton, T. J.; Wright, S. *J. Org. Chem.* **1986**, *51*, 2965.

Solvent Dependence of Carboxylic Acid Condensations with Dicyclohexylcarbodiimide[1]

Bruce J. Balcom and Nils O. Petersen*

Department of Chemistry, University of Western Ontario, London, Ontario, Canada, N6A 5B7

Received September 8, 1988

The kinetics of a model dicyclohexylcarbodiimide (DCC)–carboxylic acid condensation have been studied in six organic solvents at low concentrations of DCC and acid. The first bimolecular rate constant for acid addition to DCC (k_1), to give an *O*-acylisourea, and the second bimolecular rate constant (k_3) for acid addition to this intermediate, to give an anhydride, are both dependent on the interaction between acid molecules and solvent. These rate constants correlate extremely well with measures of the solvent's hydrogen-bond accepting ability. The rate constant for intramolecular rearrangement from the *O*-acylisourea to the *N*-acylurea (k_2) is, by contrast, independent of the solvent. Formation of dimers of the acid is not important at these low concentrations, but it appears the reaction favors formation of anhydride whenever retardation of the k_1 and k_3 rate constants is minimized. This occurs in solvents in which the acid is least soluble. There is, therefore, a delicate interplay between the conditions that favor the pathway producing anhydride: on the one hand high concentrations are favorable while on the other solvents that offer limited solubility are desirable. For synthetic purposes, where anhydride is the more useful product, a careful optimization of solubility and fast k_1 and k_3 rate constants are required.

Introduction

Dicyclohexylcarbodiimide (DCC) has, over the past 25 years, proven to be an exceptionally useful reagent.[2-4] The carbodiimide coupling reaction we have investigated is widely used in the fields of synthetic organic chemistry,[4-8] peptide synthesis,[4,9-12] enzymology[3,13-17] and polymer chemistry.[4,18-22]

(1) Funding provided through NSERC Grant A3272. B.J.B. holds an NSERC 1967 fellowship.

(2) Khorana, H. G. *Chem. Rev.* **1953**, *53*, 145.
(3) Kurzer, F.; Douraghi-Zadeh, K. *Chem. Rev.* **1967**, *67*, 107.
(4) Williams, A.; Ibrahim, I. T. *Chem. Rev.* **1981**, *81*, 589.
(5) Smith, M.; Moffatt, J. G.; Khorana, H. G. *J. Am. Chem. Soc.* **1958**, *80*, 6204.
(6) Neises, B.; Stegleich, W. *Org. Synth.* **1985**, *63*, 183.
(7) Rebek, J.; Feitler, D. *J. Am. Chem. Soc.* **1973**, *95*, 4052.
(8) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.
(9) Sheehan, J. C. Hess, G. P. *J. Am. Chem. Soc.* **1955**, *77*, 1067.
(10) Gross, E.; Meinhofer, J. *The Peptides*; Academic: New York, 1979; Vol. 1, pp 241, 261.
(11) Gross, E.; Meinhofer, J. *The Peptides*; Academic: New York, 1980; Vol. 2, pp 123, 135.
(12) Bodansky, M. *Principles of Peptide Synthesis*; Springer-Verlag: New York, 1984; pp 9, 58.
(13) George, A. L.; Borders, C. L. *Biochim. Biophys. Acta* **1979**, *87*, 59.
(14) Beechey, R. M.; Roberton, A. M.; Holloway, C. T.; Knight, I. T. *Biochemistry* **1967**, *6*, 3867.
(15) Partis, M. D.; Bertoli, E.; Griffiths, D. E. *J. Gen. Microbiol.* **1980**, *116*, 233.
(16) Georga, F. R. *Biochemistry* **1985**, *24*, 6783.

0022-3263/89/1954-1922$01.50/0