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Studies on the Synthesis and Chemical Properties of 1,2,5-Thiadiazolidine-3-one 1,1-Dioxide Derivatives: Synthesis of N-Alkylsulfamides by Cleavage Reactions of N-(4-Methoxybenzyl)- and N-(3,4-Dimethoxybenzyl)-N′-alkylsulfamides with Trifluoroacetic Acid

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We have recently reported the utility of N-alkylsulfamides **1** in the synthesis of heterocycles bearing sulfamide moiety[1]. Two general procedures have been introduced for the preparation of **1**; the monoalkylation of sulfamide itself with alkylamines in water[2] and the successive reactions of chlorosulfonyl isocyanate with formic acid or benzyl alcohol followed by alkylamines[3]. We now wish to disclose a convenient new procedure for the synthesis of **1**, which involves the acid cleavage reaction of N-(4-methoxybenzyl)- and N-(3,4-dimethoxybenzyl)-N′-alkylsulfamides **2**.

Treatment of catechol sulfate **3** with 4-methoxybenzylamine or 3,4-dimethoxybenzylamine in DMF at 0°C for 1 hr in the presence of triethylamine resulted in the formation of the sulfamate esters **4** in quantitative yields[4]. Reaction of these sulfamate esters **4** with various alkylamines in boiling dioxane afforded the unsymmetrical sulfamides **2** in 90-92% yields (see Table 1). Treatment of these sulfamides **2** with trifluoroacetic acid at rt for 3 hr and recrystallization of the resulting solid from water then produced N-alkylsulfamides **1** in 85-88% yields (see Table 1).

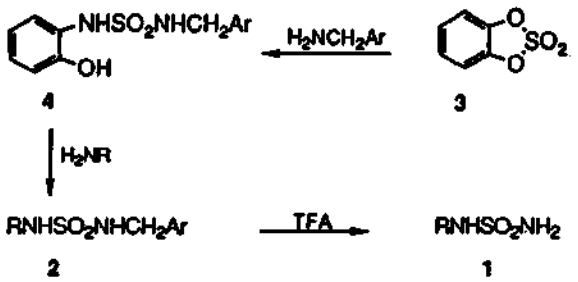

Table 1. Synthesis of Sulfamate Esters **4**, Unsymmetrical Sulfamides **2**, and N-Alkylsulfamides **1**

Compounds	Ar	R	Mp. (°C)	Yield (%)
4a	4-methoxyphenyl		116-115	98
b	3,4-dimethoxyphenyl		79- 80	97
2aA	4-methoxyphenyl	benzyl	115-116	91
aB	4-methoxyphenyl	phenethyl	110-111	90
aC	4-methoxyphenyl	3-phenylpropyl	137-138	92
bA	3,4-dimethoxyphenyl	benzyl	105-106	90
bB	3,4-dimethoxyphenyl	phenethyl	76- 78	91
bC	3,4-dimethoxyphenyl	3-phenylpropyl	89- 90	90
1A		benzyl	107-108	85
B[5]		phenethyl	68- 69	87
C		3-phenylpropyl	65- 66	88

This cleavage reaction is believed to proceed by protonation at the nitrogen first, from which the stable 4-methoxybenzyl or 3,4-dimethoxybenzyl cation is smoothly removed.

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5. Spectral data of the compound **1B** are as follows: IR (KBr) 3350, 1320, 1120 cm^{-1}; ^{1}H-NMR (MDSO-d_6) δ 2.78 (t, 2H, J=7.3 Hz), 3.07-3.14 (m, 2H), 6.56 (s, 2H), 6.95 (t, 1H, J=6.6 Hz), 7.19-7.41 (m, 5H); ^{13}C-NMR (DMSO-d6) δ 35.25, 44.26, 126.15, 128.35, 128.66, 139.37 ppm.

Selectivity Control in Chlorination of Phenol by Changings Surfactant Concentration

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For the last several years, the effect of hydrophobicity

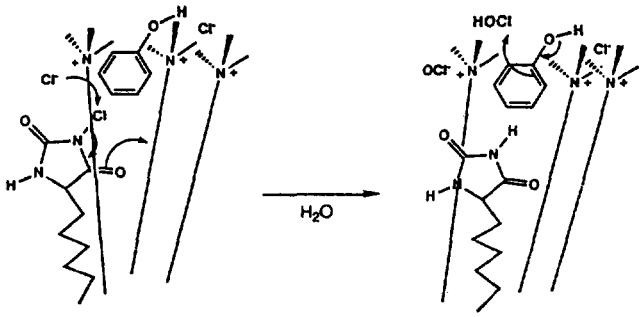
Table 1. The Effect of Surfactant Concentration in Chlorination of Phenol by N_3-Chloro-5-hexylhydantoin (C_6MCH)[a]

Surfactant	[surfactant] /10^{-3} M	ortho[c] %	para[b] %	*o/p*	Yield[c]
None[d]	0	67	33	2.03	14
CTACl	0.5	54	46	1.17	48
	1	53	47	1.13	41
	2	49	51	0.96	45
	3	42	58	0.72	43
	8	65	35	1.86	30
	10	71	29	2.45	37
	50	78	22	3.55	38
CTABr[e]	0.3	47	53	0.89	38
	0.9	44	56	0.79	27
	2.2	39	61	0.64	29
	30[f]	34	64	0.53	37
	50[f]	52	48	1.08	72

[a]Condition; 0.02 M Carbonate Buffer, pH 6.3; reaction temperature, 24±1°C; reaction time, 30 min; [phenol]=1.0×10^{-3} M, [C_6MCH]=1.0×10^{-3} M. [b]Normalized value. [c]Yields are based upon chlorinating agent used. [d]The observed ortho selectivity may due to the hydrogen bonding between phenol and C_6MCH. [e]pH 8.3. In pH 6.3 solution, bromophenol derivatives were produced even at low concentration of CTABr. [f]All of the products were bromophenols, and no chlorophenols were found.

of a micellar system on the regioselectivity in halogenation of phenol derivatives has been the subject of extensive investigations.[1] Generally, the orientation effect in a cationic micellar system is believed to be greater than that in an anionic micellar system.[2] But compared with other micellar system, no significant *o/p* selectivity in halogenation of phenol derivatives has been reported yet in a cationic micellar system.[3] This can be rationalized by the fact that the repulsion between the halogen electrophile and the cationic head group prevented the increase of *o/p* selectivity in the cationic micellar system.

We now wish to report some interesting results in the chlorination of phenol by N_3-chloro-5-hexylhydantoin[4] in a cationic micellar system (Table 1). As the concentration of CTACl surfactant was increased, the para selectivity was increase steadily until the surfactant concentration reached 3 mM. But when the concentration of CTACl is larger than 3 mM (above CMC[5]), the observed selectivity change was inverted. In CTABr micellar solution, para selectivity was also increased until the concentration of CTABr reached 2 mM. Further increase of CTABr concentration resulted in the formation of bromophenols. At high concentrations of CTABr solution (50 mM), all of the products were bromophenol derivatives and none of the chlorophenols were found. This means that the counter ions in the micellar structure participated in the bromination reaction[6], which is dependent upon the surfactant concentration. At high concentration of CTABr solution, reaction between N-chloro compound and the counter ion yielded bromine chloride.[7] Being very unstable in H_2O, bromine chloride easily yielded HOBr and Cl^-. In excess of Br^-, HOBr may be equilibrated with Br_2, and further with Br_3^- according to the following equation (Scheme 2).



Scheme 1. Schematic representation of ortho selectivity at high concentrations of CTACl micellar solution.

	Eqilibrium Constants
$BrCl+H_2O \leftrightarrows HOBr+H^++Cl^-$	2.95×10^{-5}
$HOBr \leftrightarrows OBr^-+H^+$	2.00×10^{-9}
$HOBr+H^++Br^- \leftrightarrows Br_2+H_2O$	2.27×10^{8}
$Br^2+Br^- \leftrightarrows Br_3^-$	17

Scheme 2.

The bromination of phenol was carried out by these bromine species. The existence of such bromine species was proved by the UV spectra.[8] When the UV spectra were taken at 266 nm, the absorbance was increased as the CTABr concentration was also increased, which indicated that the formation of Br_3^- was dependent on the surfactant concentration. These brominating agents were known to be more reactive than other N-chloro compounds.[9,10] As a result, chlorophenols, which is the product from N-chloro compound, could not be found at high concentrations of CTABr. However, in case of CTACl, the increase of para selectivity at relatively low CTACl concentration was mainly due to the N-chloro compound, which is hydrophobic enough to be located in the interior of the micelle. If the CTACl concentration is further increased above CMC, Cl_2 formation by N-chloro compound and Cl^- would be increased also. Cl_2 in water can be equilibrated with HOCl and OCl^- in a similar fashion to Scheme 1. At pH 6.3, the major chlorine species is HOCl[9], which would be located in the bulk phase (Scheme 1).

The relative reactivity of HOCl is known to be larger than that of N-chloro compound.[9] As a result, the increase of CTACl concentration preferred ortho selectivity, which mainly resulted from the halogenation reactions by HOCl.

Experimental

All the reactions were carried out by adding 50 μl of 0.2 M N-chloro-5-hexylhydantoin in CH_3CN into 10 ml of surfactant micellar solution containing 0.01 mM phenol. After 30 min of stirring, 0.2 g of $Mg(ClO_4)_2$ and 1 ml of 1 N HCl were added to stop the reaction and precipitate most of the surfactant molecules. After 10 ml of CH_3CN were added to the reaction mixture, saturated by NaCl, 3 μl of the upper layer were taken, and analyzed by HPLC.[11]

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11. HPLC condition; Waters Model 510 HPLC System on 30 cm×5 mm (i.d.) μ-Bondapak C_{18} column with CH_3CN-H_2O (4 : 6); flow rate, 1.2 ml/min, UV Detector (270 nm).

Difference in Effects of Appended 2-O- and 6-O-Tosyl Groups of β-Cyclodextrin on the Binding and Hydration Reaction of 1-Benzyl-1,4-Dihydronicotinamide

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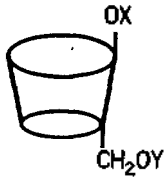
Cyclodextrins (CDs) and their derivatives have attracted great interest as enzyme models because of their ability to form inclusion complexes with great variety of guest molecules from aqueous solution.[1] The tosylated CDs are major intermediates for derivatization of CDs,[2] and show different binding affinity and catalytic effect from parent CDs.[3,4] The stability and structure of the enzyme model/substrate complexes, which are expected to depend on the configuration of the hosts, have large influences on the catalytic effects of the enzyme models.[1] Thus, information on the host structure and the clarification of the structural effects on binding and reactivity of substrates are important for designing enzyme model systems.

Recently, we have shown that the coenzyme NADH analogues, 1,4-dihydronicotinamides, form 1 : 1 inclusion complexes with β-cyclodextrin (β-CD) (**1**) and the acid-catalyzed hydration reaction of the NADH analogues is inhibited by the complexation.[5] We now report the effect of appended tosyl groups of β-CD on the binding and reaction of 1-benzyl-1,4-dihydronicotinamide (BNAH). This gives clear picture about geometry of mono-tosylated β-CD.

Mono(2-O-tosyl)-β-CD, 2-Ts-CD, (**2**) was prepared by reacting β-CD with dibutyltin oxide and then tosyl chloride/triethylamine in dry DMF.[6,7] Mono(6-O-tosyl)-β-CD, 6-Ts-CD, (**3**) was prepared from the reaction between β-CD and tosyl chloride in aqueous NaOH solution.[9]



1; X=H, Y=H
2; X=Tosyl, Y=H
3; X=H, Y=Tosyl

The hydration reaction of BNAH was monitored spectrophotometrically and obeyed pseudo-first-order kinetics with respect to BNAH[5,10] regardless of the presence of the host (**1**)-(**3**). The rate constants k_φ are summarized in Table 1. Values of k_φ vary significantly with hosts. The effects of host on k_φ are explained in terms of different reaction rates for free and host-complexed BNAH as shown in Scheme 1: we assume 1 : 1 complexation (see, below).

K is the binding constant of BNAH with host. The apparent k_φ determined at host concentration [host] is related with K, k_φ° and k_φ^{CD} by Eqn. (1).[5]