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METHYLATED CYCLODEXTRIN AND A CYCLODEXTRIN POLYMER AS CATALYSTS IN SELECTIVE ANISOLE CHLORINATION

Ronald Breslow, Harold Kohn, and Brock Siegel
Department of Chemistry, Columbia University, New York, New York 10027

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We have reported[1,2] that the reaction of anisole with HOCl in aqueous solution is modified and catalyzed by α and β-cyclodextrins (cyclohexa- and cycloheptа-amylose) Kinetic studies[2] indicated that the mechanism involves the hydrophobic binding of anisole into the cyclodextrin cavity, followed by selective donation of chlorine from one of the cyclodextrin hydroxyl groups to an aromatic ring position With anisole this selective chlorination goes exclusively to the para position (although with p-cresol a different geometry of binding results in catalytic ortho chlorination) In spite of the catalyzed exclusive para chlorination within the complex, the presence of some unbound anisole in equilibrium with the complex and the random chlorination pattern of free anisole resulted in an optimum selectivity under our previous conditions of 96% para, and 4% residual ortho, chlorination With some derivatives of the cyclodextrins we have now obtained further evidence on the mechanism of this biomimetic chlorination, and achieved even higher selectivities.

The cyclodextrins have on one side of the cavity the set of primary hydroxyls derived from C-6 of glucose, while on the other side of the cavity are the secondary hydroxyls derived from C-2 and C-3 Partial methylation of α-cyclodextrin converts it to dodecamethyl-α-cyclodextrin,[3] in which all the primary hydroxyls and all the hydroxyls at C-2 are methylated At a concentration of 10^{-2} M of dodecamethyl-α-cyclodextrin and 5 x 10^{-4} M anisole with 1 x 10^{-2} M HOCl the chloroanisoles are produced quantitatively and there is less than 1% ortho, with greater than 99% para, chloroanisole This establishes that the C-3 nydroxyl group can play the catalytically active function (although it does not exclude the possibility that other hydroxyls play a role in the unmethylated cyclodextrin). Perhaps more striking, the selectivity with dodecamethylcyclodextrin is considerably greater than that we had observed with simple α-cyclodextrin. Spectrophotometric determination indicates that K_{diss} is 8.4 x 10^{-4} M at 25 0 ± 0 1° for the anisole complex with dodecamethyl-α-cyclodextrin in water, 4.4 times as strong a binding constant as was found for α-cyclodextrin itself with anisole. This increased binding

is enough to account for the higher selectivity with the methylated derivative, assuming that chlorination within the complex is again completely specific The increased binding may indicate that the methoxyls, particularly on the primary side of the cyclodextrin, cluster to form a floor to the cavity and thus increase the hydrophobic area.[4]

An O-alkylated polymer can be produced by reacting α-cyclodextrin with epichlorhydrin under basic conditions [5] Absorption isotherm studies show that this polymer binds 4.3×10^{-2} mmoles of anisole per gram of resin from aqueous solution. This binding must also be into the hydrophobic pocket with a very similar general geometry to that in solution, since the polymer also can catalyze the selective chlorination of anisole A column of resin was loaded with anisole, then an aqueous solution of HOCl was passed through, and finally the product was washed out with tetrahydrofuran Quantitative vpc analysis, with appropriate controls, showed that the chloroanisole mixture was greater than 99% para, with less than 1% ortho. Thus, there is apparently almost no free anisole in the column, and the chlorination reaction is directed exclusively by the highly specific intracomplex mechanism. These columns can be used repeatedly with no sign of deterioration, and it seems likely that this process could be adapted for continuous flow The polymer thus combines the convenience of solid phase reaction with the highest selectivity observed for cyclodextrin derivatives in this aromatic substitution reaction

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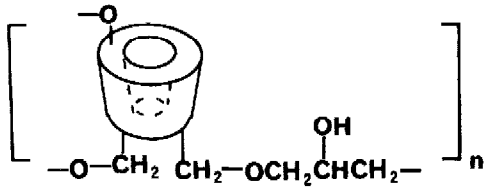

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