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Michael D. Groaning[a]; Valerian T. D'souza[a]
[a] Department of Chemistry, University of Missouri, St. Louis, Missouri

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Communication

Accelerated Transacylation of Unactivated Phenyl Esters at Physiological pH with β-Cycloaltramine

MICHAEL D. GROANING and VALERIAN T. D'SOUZA*

Department of Chemistry, University of Missouri, St. Louis, Missouri 63121

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The recently reported novel cyclodextrin, β-cycloaltramine, exhibits a 5.3×10^4 fold acceleration (compared to buffer) in transacylation of *unactivated* phenyl esters at *physiological pH* and follows saturation kinetics similar to enzymes. This acceleration is attributed to the change of the nucleophile and better binding of the substrate by this novel flexible host.

Cyclodextrins[2] have been extensively investigated in the last few decades for their binding and catalytic properties,[3,4] applications in molecular recognition,[5] self assembly,[6] and artificial enzymes.[7] Efforts to increase the catalysis of transacylation reactions by modification of cyclodextrin have received considerable attention and have seen moderate success in recent years. Among the many modifications that have been made are cyclodextrino-metal complexes,[8] artificial chymotrypsin,[9] mono imidazolyl,[10] and other mono- and difunctionalized cyclodextrins.[11] Our attempts to enhance the catalytic abilities have been directed toward the modification of all the hydroxyl groups at the 3-position of cyclodextrin by using a key intermediate, *manno* heptakis-2,3-epoxy-β-cyclodextrin, reported earlier.[12] After we published the synthesis of the first of these new cyclodextrins, (Cycloaltramine, **1**)[6d] a second compound in this series, β-cycloaltrin, was recently reported[13] without any reference to its catalytic properties. A major consideration in these systems is to determine whether the stereochemical and conformational changes accompanying the synthetic steps[14] enhance their binding and catalytic properties. We now report that **1** exhibits a substantial activity in transacylation reactions of *unactivated* phenyl esters at *physiological pH* and follows saturation kinetics similar to enzymes.

Addition of **1** (0.01 M) to a solution of *p-t*-butylphenyl acetate (in *pH* 7.26 HEPES buffer) results in a transacylation reaction with a pseudo-first-order rate constant $k_{amine} = 2.1 \times 10^{-3}$ sec^{-1} (A in Figure 1). At *pH* 7.26, transacylation of this substrate by native cyclodextrin (0.01 M) occurs with a pseudo-first-order rate constant $k_{native\ CD} = 1.4 \times 10^{-5}$ sec^{-1} (C in Figure 1) yielding $k_{amine} \backslash k_{native\ CD} = 1.5 \times 10^2$. When the same reaction is done in buffer alone, the reaction proceeds with a pseudo-first-order rate constant $k_{buffer} = 2.7 \times 10^{-7}$ s^{-1} (B in Figure 1) yielding an acceleration ($k_{amine} \backslash k_{buffer}$) of 7.7×10^3 fold. This acceleration by **1** over native cyclodextrin can be

*Corresponding author.

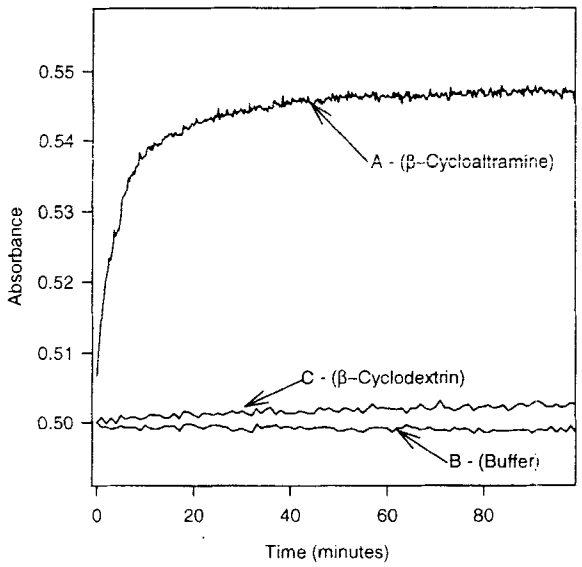


FIGURE 1 Hydrolysis of *p-t*-butylphenyl acetate by: A = β-Cycloaltramine; B = buffer; C = native β-cyclodextrin. Lines B and C have been offset on the Y-axis by 0.5 units.

attributed to two factors: the change of nucleophile and/or better binding by the flexible[15] β-cycloaltramine.

Table I compares the physical properties of various transacylation and hydrolytic systems at physiological *pH* using second-order rate constants. β-Cycloaltramine, **1**, exhibits a 5.3×10^4 fold acceleration in transacylation reactions of *p-t*-butylphenyl acetate versus the same reaction done in buffer alone. Compound **1** is 3.3 times faster for an unactivated phenyl ester than the cyclen-Co(III) complexed cyclodextrin reagent[16] under similar conditions for an activated phenyl ester (PNPA) reported by Czarnik.[8]

In order to investigate the origin of this acceleration, the rate of transacylation of *p-t*-butylphenyl acetate at various concentration in the presence of **1** was determined. This reagent follows an enzyme-type reaction scheme and gives saturation kinetics[17] suggesting that the substrate binds to **1** before the transacylation step. Michaelis-Menten analysis of these data affords a binding constant (K_m) of 4.0×10^{-3} M and a second-order equivalent rate constant ($k_{complex}/K_m$) of 6.0×10^{-1} M^{-1} sec^{-1}. This rate constant for the native cyclodextrin is determined to be 8.1×10^{-5} M^{-1} sec^{-1} which translates into a maximum acceleration of 7.4×10^3 fold for **1** over the native one. However, the change of reacting nucleophiles can account for this acceleration,[18] provided that the orientation of the substrate bound to the reagent is favorable for this reaction. The position of the amine in this system, inferred from molecular modelling studies[19] shows that the amines are pointed toward the inside of the cavity which is indeed more favorable than the hydroxyl groups of the original cyclodextrin.

Transacylation of *p-t*-butylphenyl acetate (5×10^{-5} M) in the presence of varying amounts of glucosamine (0.01–0.1 M) was followed to investigate the effects attributed to the incorporation of the new nucleophile into the system. At *pH* 7.26, this reaction follows second order kinetics with a rate constant of $k_2 = 8.4 \times 10^{-3}$ M^{-1} sec^{-1}. As can be deduced from table I, over 300 fold acceleration is obtained when the nucleophile is changed from glucose to glucosamine.

TABLE I A comparison of various transacyl and hydrolytic systems

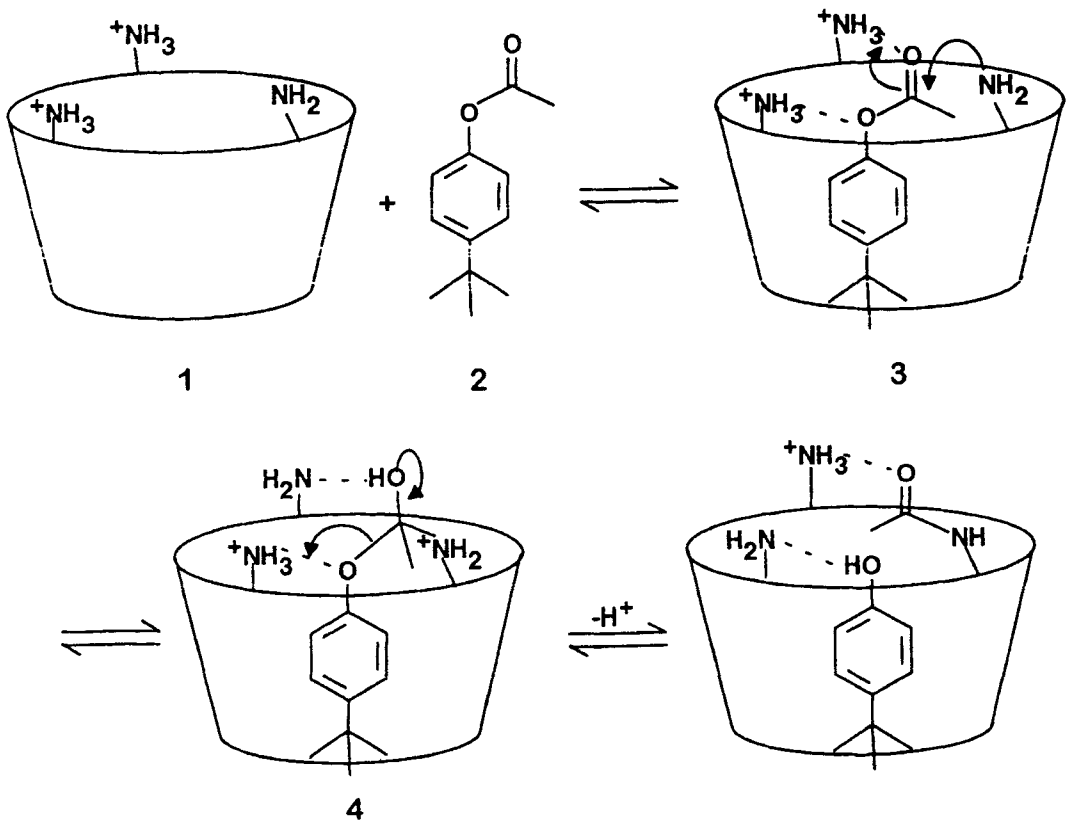
System	Substrate[a]	*pH*	$k_2 \times 10^{-2}$ $M^{-1}s^{-1}$	Acceleration
H_2O[b]	*pt*BPA	7.26	0.0011	1.0
glucose[b]	*pt*BPA	7.26	0.0023	2.1
glucosamine[c]	*pt*BPA	7.26	0.84	7.5×10^2
β-cyclodextrin[c]	*pt*BPA	7.26	0.0081	7.2
β-Cycloaltramine[c]	***pt*BPA**	7.26	60	5.3×10^4
cyclen Co(III)-cyclodextrin[d]	PNPA	7.00	18	1.6×10^4

[a]*pt*BPA = *p-t*-butylphenyl acetate, *p*NPA = *p*-Nitrophenyl acetate.
[b]Extrapolated from data provided in ref. 3.
[c]Values were determined by following the formation of phenol at 300nm spectrophotometrically.
[d]Estimated from data provided reference 8.

The second order equivalent rate ($k_{complex}/K_m$) for the transacylation in the presence of **1** is almost two orders of magnitude greater than the rate constant with glucosamine which can be attributed to the binding of the substrate to **1**.

The *pH*-rate profile for transacylation of *p-t*-butylphenyl acetate gives a negative slope suggesting a general acid catalyzed reaction. This is in contrast to the base catalyzed aminolysis normally observed with esters.[20] Kinetic-solvent-isotope effects, using D_2O gives $k_H/k_D = 1.32$, further indicating that the N-H(D) bond is broken along the reaction coordinate. A mechanism for this reaction that accounts for all these experimental facts can be written as shown in scheme 1. The substrate **2** binds to **1** to form complex **3** which is followed by a nucleophilic attack by one of the free amines on to the carbonyl group of the substrate assisted by a proton from an ammonium ion of one of the other altrose units to form a tetrahedral intermediate **4**. The acyl group is then transferred to the β-cycloaltramine to give the acylated form of **1** and the resulting phenol is released.

β-cycloaltramine also exhibits interesting substrate specificity. For example, there is no acceleration of transacylation of activated esters such as PNPA (*p*-nitrophenyl acetate) in the presence of **1**. First-order rates of aminolysis followed spectrophotometrically for both glucosamine and **1** were found to be virtually identical ($k = 6.7 \times 10^{-6}\ s^{-1} \pm 3.4 \times 10^{-7}$) and this can be explained in terms of change in the rate determining step[21,22] or absence of binding. These and other interesting mechanistic properties of **1**, such as the nature of the reactive species (monomer or dimer, state of ionization etc.), are currently under investigation.



SCHEME 1 Proposed mechanism of action of β-Cycloaltramine in hydrolysis of *p-t*-butylphenyl acetate. For the sake of clarity, only three of the seven amines are shown.

The structural and stereochemical changes that take place during synthesis of these novel cyclodextrins in which the hydroxyl groups at the 3-position are converted to other functionalities alter both their binding and catalytic abilities and extend the investigative possibilities of these system to areas that have not, as yet, been studied.

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[15] The flexible nature of this molecule is deduced from the NMR evidence as described in reference 6d.

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