moreover, by common good nucleophiles, such as aniline, pyridine, and benzylamine.

Seeking additional examples of such behavior, we have prepared salts of 2-acetyl-3-methylbenzothiazolium, a quaternary cation previously unknown.[2] Like the acetylbenzimidazolium cation, and in marked contrast to other reactive acyl compounds such as *N*-acetylpyridinium ion, *N*-acetoxypyridinium ion, and acetyl chloride, the acetylbenzothiazolium cation is stable toward deacylation by ambient atmospheric moisture, and even toward being dissolved in water as long as the pH is kept low.[3] If the pH is raised even a little, however, deacylation is very rapid indeed. The half-life is less than a minute at pH 5 and a half-second at pH 7. The hydroxide-dependent rate constant is about $1 \times 10^9$ $M^{-1}$ $min^{-1}$ (30 °C, 0.1 M NaCl). Noteworthy, as with the benzimidazolium compound[1] and with the analogous 2-acetyl-3,4-dimethylthiazolium cation,[4,5] is the complete absence of a hydroxide-independent, water-mediated deacylation. The reaction rate is linear with hydroxide from pH 7 at least to pH 3 and probably to pH below 2. Also, again as with the benzimidazole, competing nucleophiles are ignored. No trace of acetanilide is found in reaction mixtures containing aniline, and no significant rate change is seen in buffers (pH 5-6) containing aniline, pyridine, azide ion, or ammonia.

The deacylation is faster than any other hydroxide-mediated deacylations for which we have been able to find rate constants reported. Among carbon-carbon cleavages, diethyl acetylmalonate and diethyl acetylethylmalonate are reported[6] to deacylate with hydroxide constants of $1.3 \times 10^8$ and $\sim 7 \times 10^7$ $M^{-1}$ $min^{-1}$, respectively. Reaction at rates corresponding to these constants is observed only within a narrow pH range (pH 3-4). For both compounds only a pH-independent water reaction is seen below pH 3, and hydration becomes rate-determining above pH 4 so that at neutrality the observed rates are slowed several thousand fold. Published data for the cleavage of nitroacetone[7] can be interpreted to yield a hydroxide rate constant about $1 \times 10^8$ $M^{-1}$ $min^{-1}$ at pH 4-5, but there is no pH-rate study and hence no certainty that this interpretation is valid. Other carbon-carbon cleavages are much slower. For the 2-acetyl-3,4-dimethylthiazolium cation Bruice[4] reports $k^{OH} = 5.64 \times 10^6$ $M^{-1}$ $min^{-1}$ at 30 °C over a wide pH range. A similar value may be deduced from the rate constant of $13.6 \times 10^6$ $M^{-1}$ $min^{-1}$ at 25 °C reported by Lienhard[5] for cleavage of the ketone hydrate. The 2-acetyl derivative of thiamin pyrophosphate cleaves at almost exactly the same rate.[11]

The fastest acyl-X cleavages appear to be those of *N*-acetylpyridinium ions, studied[8] as transient intermediates in the pyridine-catalyzed hydrolysis of acetic anhydride. *N*-Acetyl-4-picolinium ion has $k^{OH} = 1.6 \times 10^6$ $M^{-1}$ $s^{-1}$ (i.e., $1 \times 10^8$ $M^{-1}$ $min^{-1}$). The $k^{OH}$ for *N*-acetylpyridinium may be double this. Only a narrow pH range was studied. The pH-independent water reaction dominates below pH 4, and there is no data above pH 5. The most reactive acyl-X compound studied directly, the *N*-acetoxypyridinium cation,[9] is some orders of magnitude less reactive, $k^{OH} = 5.7 \times 10^5$ $M^{-1}$ $min^{-1}$. Data, again, is only for a narrow pH range (9-10), and again the pH-independent water reaction dominates below pH 8. There seems to be no good pH-rate data published for acetyl chloride, but since its hydrolysis is catalyzed by pyridine, it would seem that the spontaneous deacylation must be slower than that of the *N*-acetylpyridinium ion. Other acyl-X compounds such as acetic anhydride and 2,4-dinitrophenyl acetate are much less reactive.

A detailed study of the kinetics and mechanism of hydration and deacylation of the quaternary 2-acetylheterocyclonium ketones is in hand and will be reported soon. For the present, however, the following conclusions appear justified:

1. The hydroxide-mediated deacylations are remarkably fast and reaction is linear with hydroxide throughout a wide pH range.
2. Neither traditional "good" nucleophiles nor water competes with hydroxide, which is to say, no hydroxide anomaly[9,10] is seen.
3. Deacylation rates relate not at all to the quality of the leaving group as indicated by the $pK_a$ of its conjugate acid. The 3-methylbenzothiazolium carbanion (conjugate acid $pK_a \sim 16$) departs 1000 times more readily than pyridine *N*-oxide (conjugate acid $pK_a = 2$), a rate discrepancy, viewed simplistically, in excess of $10^{17}$-fold.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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(3) Exposed to atmospheric humidity greater than 80%, the trifluoromethanesulfonate undergoes reversible hydration to *gem*-diol. The chloride hydrate (*gem*-diol) crystallizes from 10% hydrochloric acid and is stable indefinitely. In water at pH below 2, a slow rearrangement occurs with ring expansion to a thiazinone (ref 2). This is without relevance to deacylation, which would have a half-life of some 15 h at pH 2.
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## Potent, Broad-Spectrum Inhibition of Glycosidases by an Amidine Derivative of D-Glucose

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Interest in glycoside-cleaving enzymes has been stimulated by the finding that plants and microorganisms produce a variety of monosaccharide-like alkaloids which are potent glycosidase inhibitors.[1] Many such substances have been useful in unraveling how glycosidases catalyze hydrolysis,[2] and some show promise in treating diabetes[3] or as novel antiviral[4] and anticancer[5] agents. Their mode of action is predicated on a generally accepted catalytic mechanism (Figure 1)[6] for enzymes that hydrolyze with retention of configuration. That mechanism involves (a) protonation of the glycosidic oxygen and fragmentation with departure of the aglycon ROH producing (b) a transient, point-charge-stabilized oxocarbonium ion **1** which subsequently collapses to (c) a glycosyl-enzyme intermediate that eventually undergoes hydrolysis at the active site. Protonated inhibitors like 1-deoxynojirimycin (1-dNM) **2** and 1-deoxymannonojirimycin **3** apparently mimic the corresponding gluco- or mannopyranosyl cation.[2,7]

In fact, however, glucose analogue **2** does not resemble the flattened chair conformation of cation **1** particularly well. We now report the first synthesis of (+)-**4**·HCl, the amidine analogue of D-glucose, which combines the correct charge and conformation of glucosyl cation **1**.[8] The $sp^2$-hybridized anomeric carbons in **4** and its *N*,*N*-dimethyl derivative (+)-**5** also accommodate both the endocyclic nitrogen of 1-dNM and the exocyclic amine group of β-D-glucosylamine, another highly effective glucosidase inhibitor.[9] Besides being a potent inhibitor of β-glucosidase, amidine

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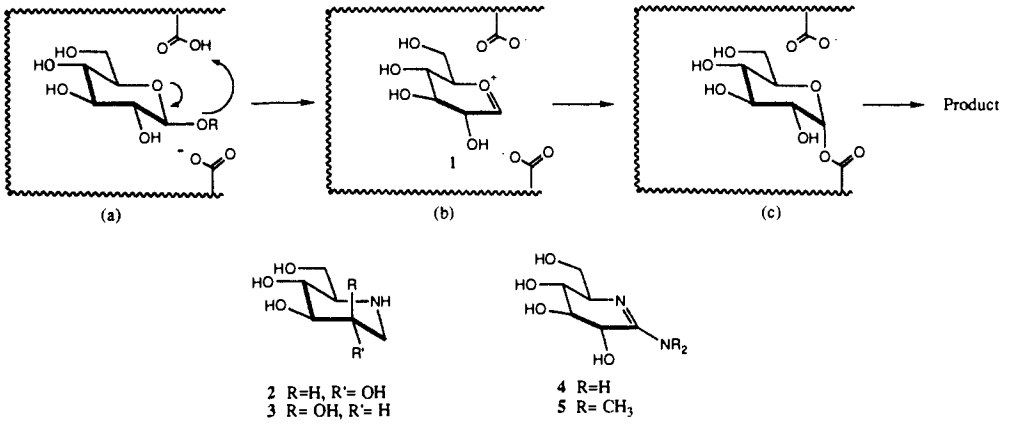


Figure 1.

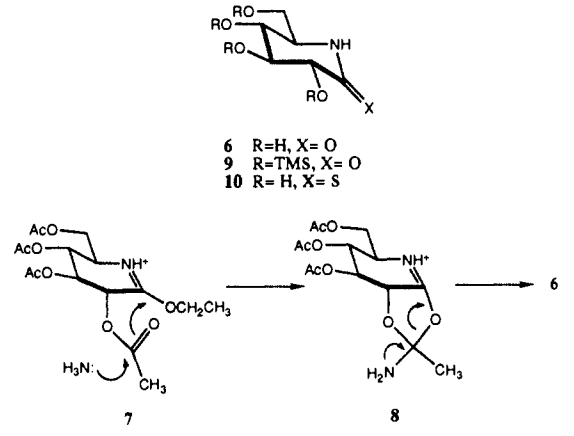


Figure 2.

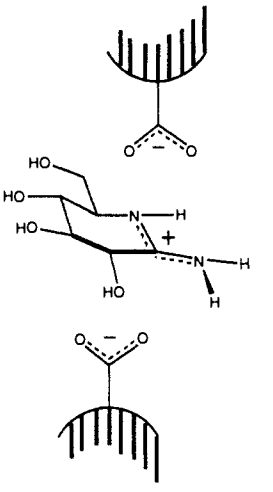

Figure 3.

4 exhibits an unexpected and unprecedented range of activity against gluco-, manno-, and galactosidases.

The synthesis of 4 and 5 began with readily available D-gluconolactam 6 (Figure 2).[10] Attempts to prepare 4 from imino ether 7, obtained from 6 after acetylation and treatment with Meerwein's salt ($Et_3OBF_4$, $CH_2Cl_2$, room temperature 36 h), were unsuccessful. Exposure of 7 to excess anhydrous ammonia under scrupulously dry conditions ($NH_3$–$CH_3OH$, $NH_3$–$CHCl_3$, anhydrous liquid $NH_3$) led only to D-gluconolactam 6 with no trace of the desired amidine. Initial attack of ammonia apparently occurred at the allylic acetate of 7, with subsequent intramolecular nucleophilic addition/elimination forming 8. Breakdown of 8 as shown and exhaustive ammonolysis thus furnished 6.

To circumvent these problems, we first silylated 6 to 9 and then converted 9 to the corresponding thionolactam 10 using Lawesson's reagent.[11,12] Treatment with ammonia-saturated $CH_3OH$ afforded amidine 4 as a moisture-sensitive oil. Acidification with anhydrous HCl–$CH_3OH$ gave the stable hydrochloride salt 4·HCl (80%), along with small quantities of 6 (10–20%). The corresponding *N,N*-dimethylamidine salt 5·HCl could be prepared free of 6 by reaction of thionolactam 10 with methanolic dimethylamine under similar conditions (85% yield).

Crude amidine salts 4·HCl and 5·HCl, while extremely labile to base, are stable to water and can be chromatographed on silica (20:4:1 $CH_3CN$–$H_2O$–HOAc) to furnish analytically pure samples of 4·HOAc and 5·HOAc.[12] Infrared comparison of free 4 with several model compounds[13] indicates a preference for the endocyclic tautomer 4 shown.[14] Moreover 4 furnishes 5 (65%) when exposed to anhydrous methanolic dimethylamine.

Like 1-dNM 2, amidine 4 is a potent competitive inhibitor of sweet almond β-glucosidase (β-glu). Whereas 1-dNM exhibits pH-dependent binding,[15] inhibition by 4 is independent of pH between 4.5 and 7.0. Under steady-state conditions (*p*-nitrophenyl-β-D-glucopyranoside as substrate, $K_M$ = 2.1–3.5 mM), $K_I$ for 4 is 8 ± 5 μM over this range while $K_I$ for 2 varies from 370 to 18 μM.[15] Since 4 is clearly protonated over the pH range studied,[16] our findings suggest that it is also the protonated form of 1-dNM that interacts with unprotonated β-glu, an issue left unresolved in past studies with 2.[15,17] The corresponding *N,N*-dimethylamidine 5 is somewhat less potent than 4 against β-glu ($K_I$ = 83 ± 5 μM), although neither 4 nor 5 exhibits the slow binding characteristic of 1-dNM.[18]

Amidines 4 and 5 also interact strongly with mannose and galactose processing enzymes. Against jackbean α-mannosidase, 4 is a powerful competitive inhibitor ($K_I$ = 9 ± 1 μM at pH 5.0, 37 °C; 4–5-fold better binding than 5), perhaps because $A_{1,2}$ strain between the exocyclic $NR_2$ and C2 hydroxyl groups in 4 makes the all-axial half-chair conformer less unfavorable. Recent cal-

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(17) The activity of β-glu depends on two ionizing groups having $pK_a$'s of 4.4 and 6.7.[15] Amidine 4·$H^+$ must interact electrostatically with the former group, while the pH-dependent behavior of 2·$H^+$ reflects interaction with the less acidic residue.

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culations on the mannopyranosyl cation suggest that its triaxial half-chair conformation is energetically preferred and that most potent mannosidase inhibitors share its binding topography.[19] However, this rationale does not explain why **4** and **5** are as active against bovine β-galactosidase as against β-glu, judging from comparative $IC_{50}$ studies (no $K_I$'s determined). These findings contrast dramatically with findings for 1-dNM and other known glucosidase inhibitors which have relatively little effect on manno- and galactosidases.

With their saccharide-like structures and resonance-stabilized, partially positively charged anomeric carbons, amidinium ions **4**-$H^+$ and **5**-$H^+$ represent ideal mimics of the hexopyranosyl cations implicated in enzymic glycoside hydrolysis. As such, their activity against a cross section of glycosidases indicates that recognition and binding of this common transition-state structure, involving favorable electrostatic interactions with one or both active-site carboxylates[20] (Figure 3), overrides any modest stereochemical discrimination which the resting enzymes make between isomeric hexose residues.

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**Supplementary Material Available:** Full experimental details (including physical properties and spectral and analytical data) for the preparation of **4** and **5** plus kinetic data from enzymatic assays with **4** and **5** (10 pages). Ordering information is given on any current masthead page.

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## Solubilizing the Thallium–Platinum Unit of $Tl_2Pt(CN)_4$. Preparation and Use of a New Crown Ether/Phosphine Hybrid Ligand for Linking Main-Group and Transition-Metal Ions

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$Tl_2Pt(CN)_4$,[1,2] which has an intense blue luminescence when irradiated in the ultraviolet range, has a novel structure that distinguishes it from other crystalline inorganic compounds derived from $Pt(CN)_4^{2-}$.[3] Generally, these involve a columnar structure with Pt···Pt distances ranging from 3.09 to 3.75 Å, whereas $Tl_2Pt(CN)_4$ forms discrete, well-separated pseudooctahedral units in which the platinum is coordinated to thallium (Pt–Tl distance, 3.140 (1) Å) and the thallium is monocoordinate. $Tl_2Pt(CN)_4$ is soluble only in very polar solvents (water, dimethyl sulfoxide) where it dissociates into $Tl^+$ and $Pt(CN)_4^{2-}$ ions and loses the luminescence observed in the solid state. We are interested in the general problem of designing complexing agents that allow the transfer of part or all of such solid-state materials into soluble compounds that can be manipulated and studied by typical coordination-chemical techniques. In this case, the Tl–Pt bond is the essential unit that we sought to preserve and solubilize. To that end, we have prepared the new ligand, crown-$P_2$ (**1**) (Scheme I).

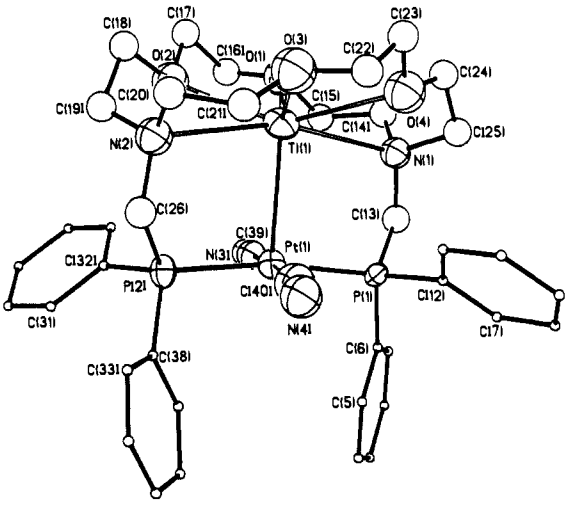
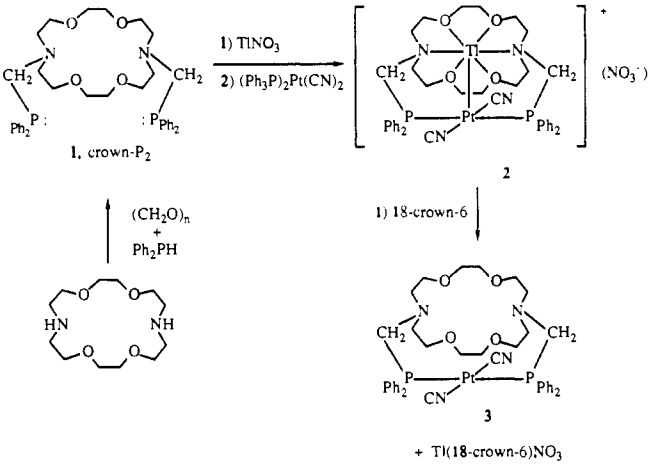



**Figure 1.** A perspective view of one of the cations in $[Tl(crown\text{-}P_2)Pt(CN)_2]NO_3$ showing 50% thermal contours and uniform, arbitrarily sized circles for the carbon atoms of the crown ligand. Selected bond distances (Å): Pt–Tl, 2.911 (2), 2.958 (2); Pt–P(1), 2.343 (8), 2.312 (11); Pt–P(2), 2.329 (8), 2.333 (10); Tl–O(1), 2.75 (2), 2.77 (3); Tl–O(2), 2.77 (2), 2.91 (2); Tl–O(3), 2.77 (2), 2.77 (2); Tl–O(4), 2.76 (2), 2.87 (2); Tl–N(1), 3.14 (2), 3.05 (2); Tl–N(2), 3.01 (2), 2.98 (2). Bond angles (deg): P(1)–Pt–P(2), 171.0 (3), 172.0 (3); P(1)–Pt–C(39), 85.4 (7), 79.9 (13); P(1)–Pt–C(40), 93.3 (8), 97.7 (11); P(2)–Pt–C(39), 95.4 (7), 100.5 (13); P(2)–Pt–C(40), 85.0 (8), 81.4 (11); Tl–Pt–P(1), 92.8 (2), 92.4 (2); Tl–Pt–P(2), 96.2 (2), 95.5 (3); Tl–Pt–C(39), 89.1 (9), 88.6 (13); Tl–Pt–C(40), 96.4 (11), 94.9 (10).

**Scheme I**




The aza-crown portion of **1** should create a suitable environment for the thallium ion while phosphorus atoms should be able to substitute for cyano ligands in $Pt(CN)_4^{2-}$. These should not produce a major perturbation of the electronic structure at the platinum. The size of the aza-crown portion situates the two phosphorus atoms so that they comfortably span trans coordination sites on a transition metal, and the facile inversion at nitrogen allows the two phosphorus donors ready access to either side of the macrocycle during complex formation. The methylene linkage between the aza-crown portion and the phosphorus atoms provides the proper spacing to accommodate the Tl–Pt moiety. Moreover, **1** is readily prepared in high yield in a one-step process.[4]

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