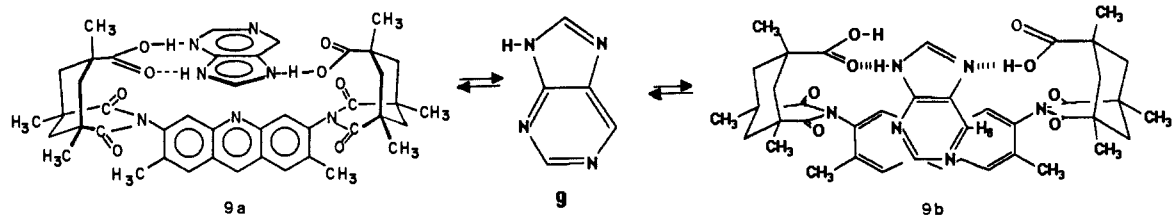
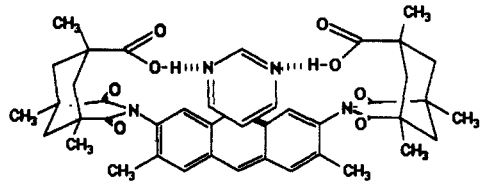


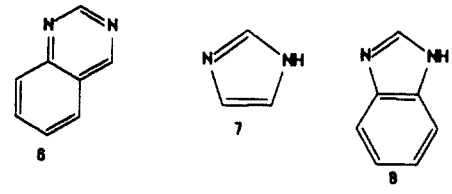
(2)

subunits in the receptor and substrate is revealed by *upfield*[3] shifts in **3**. Accordingly, the parallel arrangement of aromatics, shown in **3a**, is indicated. The diacid functions as a *molecular chelate* that positions the substrate for optimal stacking interactions. With phenazine **4**, this geometry creates steric effects involving the carbonyl oxygen of the carboxyl and the peri hydrogens of the remote (unstacked) ring and results in reduced binding. The chemical shifts observed[3] for these protons in the complex **4a** are those expected for a system showing rapid exchange between two stacking sites.

Chelation of pyrimidine **5** is slightly less favorable than that of **2** even though **5** is a stronger base and stacking interactions

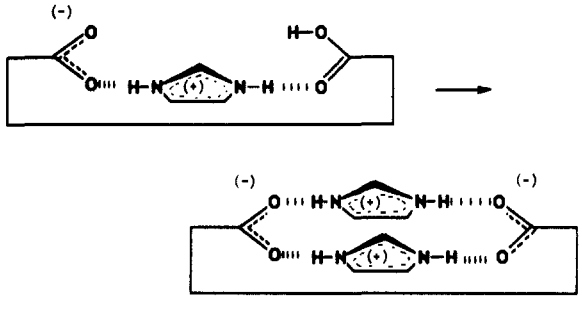


5a



can be seen in its complex with the receptor.[3] The reduced affinity of pyrimidine must be attributed to its shape: The N–N distance of about 2.5 Å is 0.3 Å shorter than in pyrazine and the orientation of the lone pairs is inferior for complexation, at least if idealized, linear hydrogen bonds are assumed. Again, the benzo derivative quinazoline **6** shows improved binding.

Yet another type of binding interaction available to **1** is revealed in its complexation with imidazole **7**, a heterocycle that can act as both hydrogen bond donor and acceptor. Here, curvature[5] of the plots indicated the binding of two molecules of **7**, with $K_2 \approx K_1$. The complexation of this relatively strong base probably involves some ionization (eq 1), a process which should improve



(1)

the hydrogen-bonding capabilities of the 1:1 complex: the carboxylate becomes a better lone pair donor while the acid becomes a better proton donor.[6] Even so, the common test for cooperativity, the Hill plot,[7] showed a slope of 0.4 indicating that the binding of a second imidazole was a factor of 20 times less favorable than binding the first. This result is most likely due to electrostatic repulsion between the two bound imidazolium ions. With the benzo derivative **8** 2 equiv of the amine were bound but somewhat less effectively and again without cooperativity. Even so, it should be possible to engineer cooperativity into this system by selecting substrates that minimize repulsions in the 2:1 complex.[8]

Finally an intramolecular competition between the two heterocyclic nuclei imidazole and pyrimidine was staged by examining the mode of binding to purine **9**. Here, as with **2**, upfield shifts are observed for the protons lining the cleft of the receptor and modest shifts are observed in the pyrimidine nucleus. These changes are best accommodated by contributions from both the perpendicular arrangement **9a** and the stacking of **9b** (eq 2) rather than direct chelation of the pyrimidine nucleus.

In summary, the arrangement of carboxyl groups and the aromatic surface of the model receptor present a number of binding possibilities to diamines. We are currently exploring the catalytic advantages offered by the convergent functionality of **1**.

Acknowledgment. We are grateful to the National Institutes of Health for financial support of this research.

(3) Upfield shifts (ppm) observed in the diamine portions of the various complexes: **2a** (none); **3a** ($H_{5,8}$ 0.1; $H_{6,7}$ 0.25); **4a** ($H_{2,3,7,8}$ 0.1); **5a** (H_5 0.15); **6a** (H_5 0.2, H_7 0.15, H_8 0.1); **7a** ($H_{4,5}$ 0.45); **8a** ($H_{4,7}$ 0.51, $H_{5,6}$ 0.53); **9a** (H_2 0.13, H_6 0.18).

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Facile Enzymatic Preparation of Monoacylated Sugars in Pyridine

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Regioselective modification, e.g., acylation of sugars, is a fundamental and difficult task in organic chemistry.[1] Even preferential acylation of primary over secondary hydroxyl groups can only rarely be efficiently carried out with free sugars;[1,2] this

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Table I. Porcine Pancreatic Lipase Catalyzed Transesterifications between Various Sugars and Trichloroethyl Carboxylates in Pyridine[a]

sugar (mmol)	trichloroethyl ester (mmol)	vol of pyridine, mL	conversion of sugar, %[b]	regioselectivity, %[c]	product[d]	isolated yield, g (% of theor)[e]
glucose (33)	butyrate (99)	75	62	82	6-*O*-butyrylglucose[f]	2.1 (50)
glucose (11)	acetate (33)	25	50	85	6-*O*-acetylglucose[f,g]	0.8 (76)
glucose (11)	caprylate (33)	25	40	84	6-*O*-capryloylglucose[f,h]	0.7 (57)
glucose (11)	laurate (33)	25	40	95	6-*O*-laurylglucose[i]	1.4 (91)
galactose (3.9)	acetate (25)	50	100	95	6-*O*-acetylgalactose[f,j]	0.5 (60)
mannose (33)	acetate (53.5)	25	38	100	6-*O*-acetylmannose[k]	2.4 (85)
fructose (11)	acetate (33)	25	47	100[l]	1-*O*-acetylfructose[m]	0.5 (60)
					6-*O*-acetylfructose[n]	0.2

[a] The experimental protocol was the same as described in the text for glucose and **1**, except that 6 g of lipase[9] was used in all other cases. [b] Determined by GC.[10] [c] Defined as the ratio of the GC peak area corresponding to the indicated main product to that of all the products formed after a 2-day enzymatic reaction. [d] Unless stated otherwise, the sugar esters were crystallized from ethanol (acetates) or ethyl acetate containing 5% ethanol (glucose caprylate and laurate). Both crystalline sugar esters and those obtained as oils (6-*O*-acetylated mannose and fructose) were 100% pure by GC and TLC. The position of acylation in all products was established by ^{13}C NMR. The NMR spectra of acetylated galactose, mannose, and fructose were compared, using the same rationale as with glucose esters,[12] to those of the free sugars (Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem. Biochem.* **1983**, *41*, 27–66). [e] Calculated taking into account the degree of conversion and the regioselectivity achieved. [f] Crystallized as the pure (by GC) α-pyranose derivative as determined by ^{13}C NMR. [g] The product had mp 143 °C and $[\alpha]_D^{30}$ +50.6° (*c* 0.7, H_2O, equil) as compared to the literature values of 146 °C and +53° (H_2O, 30 min), respectively (Frohwein, Y. Z.; Leibowitz, J. *Chem. Abstr.* **1963**, *59*, 15363a). [h] Mp 128 °C, $[\alpha]_D^{30}$ +55.7° (*c* 0.5, pyridine, equil). [i] Mp 127 °C, $[\alpha]_D^{30}$ +59.8° (*c* 0.5, pyridine, equil). [j] The position of acylation was determined as described in footnote *d* and in: Szurmai, Z.; Liptak, A. *Carbohydr. Res.* **1982**, *107*, 33–41. Mp 135–138 °C, $[\alpha]_D^{30}$ +59.8° (*c* 0.6, H_2O, equil). [k] $[\alpha]_D^{30}$ +14.7° (*c* 1.5, H_2O, equil). [l] Refers to the sum of the two acetylated primary OH groups, at C-1 and C-6. [m] Crystallized as the pure (by GC) β-pyranose derivative (by ^{13}C NMR) with mp 137–138 °C and $[\alpha]_D^{30}$ −65.5° (*c* 0.5, H_2O, equil). [n] The oily product was a mixture of α and β anomers of the furanose derivative (by ^{13}C NMR) and had $[\alpha]_D^{30}$ +6.0° (*c* 0.5, H_2O, equil).

usually requires protected sugars,[1-3] thereby necessitating cumbersome protection[1,2] and deprotection[4] steps.

Recently, we have discovered that lipases can vigorously catalyze different reactions in organic solvents.[5] One of these reactions, transesterification, has been used for stereospecific[6] and regiospecific[7] enzymatic acylation of hydroxyl groups in alcohols. In the present work, that approach has been successfully employed for a one-step, preparative acylation of primary hydroxyl groups in various unprotected monosaccharides.

We dissolved 6 g of α-D-glucose in 75 mL of warm anhydrous pyridine,[8] followed by addition of 15 mL of 2,2,2-trichloroethyl butyrate (**1**) and 18 g of dried[8] porcine pancreatic lipase.[9] The suspension was shaken at 250 rpm and 45 °C; periodically aliquots were withdrawn and analyzed by gas chromatography.[10] The glucose peak (transformed with time into a double peak corresponding to α and β anomers) gradually decreased, while two new double peaks, a major and a much smaller one, appeared. After 2 days (62% of glucose reacted) the reaction was stopped, the enzyme removed by filtration,[11] the solvent evaporated, the unreacted **1** extracted with toluene, and the remainder extracted with hot acetone. Following subsequent silica gel column chromatography of the extract (ethyl acetate–MeOH–H_2O, 100:10:1, as the solvent), the compound corresponding to the main peak in GC was crystallized from ethyl acetate. The crystalline product (2.1 g, 100% purity by GC, mp 116–117 °C, $[\alpha]_D^{30}$ +45.3° (*c* 1, H_2O)) was identified by ^{13}C NMR[12] and GC–MS[12] as 6-*O*-butyrylglucose. Thus, in the transesterification reaction between glucose and **1**, lipase exhibits an overwhelming preference toward acylation of the primary hydroxyl group in the sugar (the first entry in Table I).

The above enzymatic acylation in pyridine accelerated upon an increase of the temperature (from 25 to 45 °C) as well as the concentrations of lipase,[13] glucose, or **1**. The rate of the lipase-catalyzed transesterification decreased when less activated esters[14] than **1** were used: the reactivities of 2-monochloroethyl and ethyl butyrates were approximately half and one-sixth of that of **1**, respectively. D- and L-glucoses were equally reactive. Replacement of **1** in the enzymatic transesterification with trichloroethyl esters[14] of other carboxylic acids resulted in incorporation of other acyl moieties (from acetyl to lauryl) in the C-6 position of glucose; as one can see in Table I (entries 2–4), millimole quantities of crystalline glucose monoesters were prepared.

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(8) Both pyridine (one of a few organic solvents capable of dissolving sugars) and the enzyme were dried prior to use to eliminate hydrolysis of **1** (because of this hydrolysis the enzymatic acylations reported herein are not feasible in water). Pyridine was distilled over KOH and stored in a closed bottle in the presence of 3-Å molecular sieves. The lipase powder was evacuated for 3 days, which decreased its water content from 3.6% to 0.5% (measured by the optimized Fischer method: Laitinen, H. A.; Harris, W. E. *Chemical Analysis*, 2nd ed.; McGraw-Hill: New York, 1975; pp 391–363).

(9) The enzyme (EC 3.1.1.3) was purchased from Sigma and had a specific activity of 11 olive oil units/mg solid. The seemingly high amoung of lipase used in our experiments is misleading as the commercial preparation employed was crude (less than 1% purity) to keep the cost down (5 cents/g). Since all enzymes are insoluble in pyridine, lipase was present in pyridine solutions as a suspension.

(10) Sugars in all reaction mixtures were derivatized with 1,1,1,3,3,3-hexamethyldisilazane (Sweeley, C. C.; Bentley, R.; Makita, M.; Wells, W. W. *J. Am. Chem. Soc.* **1963**, *85*, 2497–2507) prior to capillary GC analyses.

(11) Lipase completely inactivated during this conversion, presumably due to dehydration. When the recovered enzyme was assayed potentiometrically (using a pH-stat) with respect to hydrolysis of tributyrin in water, it was nearly as active as the initial preparation. Furthermore, when freeze-dried from an aqueous solution, the previously inactivated lipase sample was again active in pyridine.

(12) The strategy of the ^{13}C NMR analysis was the same as previously described (Yoshimoto, K.; Itatani, Y.; Tsuda, Y. *Chem. Pharm. Bull.* **1980**, *28*, 2065–2076). The only difference between the NMR spectrum of the isolated product and that of authentic glucose (both in D_2O, tetramethylsilane used as an external reference) was a 2.5 ppm downfield shift of the two peaks corresponding to C-6 in α and β anomers and a 2.7 ppm upfield shift of the two peaks corresponding to C-5 in α and β anomers. As shown in the above reference, these shift values are characteristic and virtually independent of the nature of the acyl moiety and the solvent. The monoester composition of the product was also confirmed by its saponification which revealed that 1 mol of NaOH was consumed in the hydrolysis of 1 mol of the product. The GC–MS analysis of 6-*O*-butyrylglucose was conducted following the general strategy of DeJongh et al. (DeJongh, D. C.; Radford, T.; Hribar, J. D.; Hanessian, S.; Bieber, M.; Dawson, G.; Sweeley, C. C. *J. Am. Chem. Soc.* **1969**, *91*, 1728–1740).

(13) No appreciable acylation took place in the absence of the enzyme or in the presence of porcine pancreatic lipase irreversibly preinactivated with the active center specific reagent diethyl *p*-nitrophenyl phosphate (Maylie, M. F.; et al. *Biochim. Biophys. Acta* **1969**, *178*, 196–198).

(14) All esters were synthesized from the corresponding acyl chlorides and alcohols (Steglich, W.; Hofle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981).

The generality of the synthetic strategy developed was then tested with other sugars. The monosaccharides D-galactose, D-mannose, and D-fructose were all enzymatically acylated in pyridine in a regioselective manner (entries 5-7 in Table I): in the first two cases, by far the main products were the 6-*O*-acyl derivatives, while in fructose the two primary hydroxyl groups displayed comparable reactivities.[15] The methodology described in this work can be applied to efficient and selective enzymatic production of sugar monoesters to replace existing multistep chemical procedures.[1,2]

(15) The disaccharides sucrose, lactose, and maltose had very low reactivities in the porcine pancreatic lipase catalyzed transesterification with **1**, probably due to steric hindrances.

(16) This work was financially supported by W. R. Grace & Co.

Carbon-Hydrogen Bond Activation by Ruthenium for the Catalytic Synthesis of Indoles

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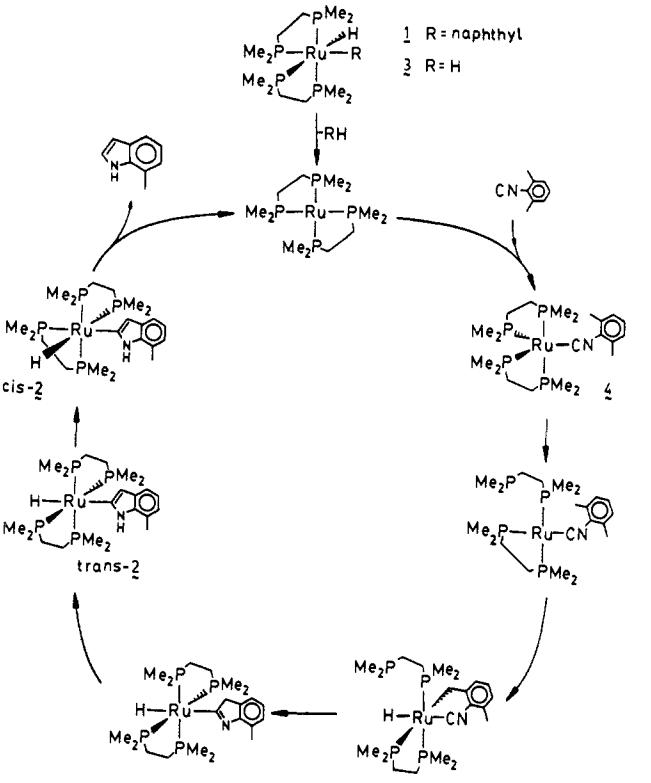
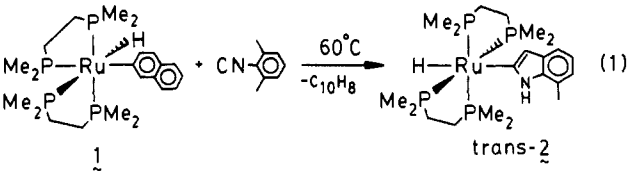
The intramolecular cyclometalation of sp^3 hybridized carbon-hydrogen bonds in ligand alkyl groups is well documented in transition-metal chemistry.[1] Recent studies have demonstrated the feasibility of intermolecular activation of sp^3 hybridized carbon-hydrogen bonds in free alkane molecules, which has stimulated a search for the functionalization of the C-H bond in a catalytic fashion.[2] We report here the activation of benzylic sp^3 hybridized C-H bonds and their catalytic conversion into an indole product using an isocyanide moiety to trap the activated species.

$Ru(DMPE)_2(naphthyl)H$ (**1**) was the first reported homogeneous metal complex to undergo reversible activation of arene and certain activated aliphatic C-H bonds.[3] We have found that thermolysis of **1** in C_6D_6 solution in the presence of 1 equiv of 2,6-xylyl isocyanide at 60 °C for 24 h results in the quantitative formation of naphthalene and a new species in which the ^1H NMR spectrum indicates a *trans*-$Ru(DMPE)_2HX$ configuration.[4] Only one of the xylyl methyl groups remains intact at δ 2.537 and the aromatic hydrogens of the isocyanide ligand appear as an asymmetric ABC pattern. A broad resonance is observed at δ 7.342

Scheme I

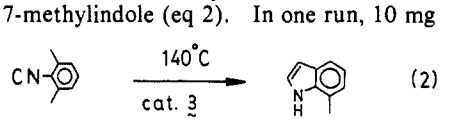


and an olefinic singlet is seen at δ 6.082. These data are consistent with the formation of a 2-substituted 7-methylindole ring and the formulation of the product as *trans*-$Ru(DMPE)_2[2$-(7-methylindole)]H (*trans*-**2**), isolated as yellow-orange crystals in 77% recrystallized yield (eq 1). Confirmation of the presence of an indole ring was obtained from an X-ray structural determination of *trans*-**2**.[5]



(1)

We have also discovered that thermolysis of 2,6-xylyl isocyanide in the presence of ~1 equiv of $Ru(DMPE)_2H_2$ (**3**) (140 °C, 24 H) in a sealed tube results in the catalytic conversion of the isocyanide into free 7-methylindole (eq 2). In one run, 10 mg



(2)

of **3** and 5 mg of 2,6-xylyl isocyanide (1:1.5 ratio) in 0.6 mL of C_6D_6 were heated for 25 h at 140 °C in a sealed tube. A ^1H NMR spectrum showed a 98% NMR yield of free 7-methylindole and no change in the quantity of **3**.

As little as 20 mol % of **3** is effective as a catalyst, although a competing metal-catalyzed dead-end side reaction is now observed. With low catalyst/isocyanide ratios, a competitive isocyanide dimerization to form a product in which the isocyanide inserts into the N-H bond of 7-methylindole in a 1,1 fashion is seen (eq 3). This dimer is apparently formed reversibly since continued heating at 140 °C ultimately results in the overall conversion of the 2,6-xylyl isocyanide into 7-methylindole in >90% yield.[6] Reaction of 50 mg of 2,6-xylyl isocyanide with 30 mg

† A.P. Sloan Fellow, 1984-1986. Camille and Henry Dreyfus Teacher Scholar, 1985-1987.

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(4) ^1H NMR of *trans*-**2** in C_6D_6: δ 7.342 (br s, 1 H); 7.650 (d, J = 8.5 Hz, 1 H); 7.211 (t, J = 7.2 Hz, 1 H); 6.897 (d, J = 7.3 Hz, 1 H); 6.082 (s, 1 H); 2.537 (s, 3 H); 1.450 (m, 4 H); 1.280 (m, 4 H); 1.230 (s, 12 H); 1.183 (s, 12 H); -12.742 (quint, J = 23.2 Hz, 1 H). Mass spectrum (75 eV): 532 (M^+), 531, 402 (M^+ - 130), 401 (M^+ - 131), 131 (M^+ - 401), 130 (M^+ - 402). IR (KBr): 1747, 1419, 1344, 1281, 941, 923, 887, 840, 788, 774, 738, 723, 700, 639 cm^{-1}. Anal. ($RuP_4NC_{21}H_{41}$): C, H, N.

(5) Thick yellow plates of *trans*-**2** crystallized in space group $Cmc2_1$ with Z = 4. Full-matrix anisotropic refinement converged at R_1 = 0.0302, R_2 = 0.0404. The indole lies in a crystallographic mirror plane with unique C_{indole}-Ru-P angles of 93.5° and 95.2°.

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