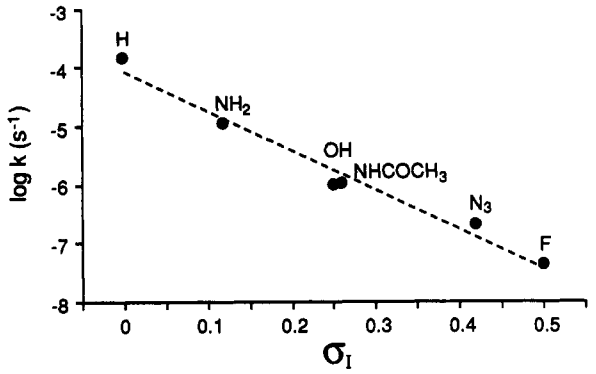

Figure 1. Plot of the log of the first-order rate constants for the pH-independent hydrolysis of the 2′-substituted nicotinamide arabinosides at 37 °C against the inductive σ constant (σ_I).

measure of the change in electron density at the reaction center during bond cleavage and are similar in sign and magnitude to ρ_I values from model reactions involving putative cationic intermediates.[16,17] Therefore, our results are consistent with a dissociative mechanism that involves an intermediate with substantial oxocarbocationic character as outlined in Scheme Ib. A dissociative mechanism is also supported by secondary deuterium kinetic isotope effects[18] and structure–reactivity studies of nucleotides with 3-substituted pyridines as leaving groups.[19]

Because the observed rate constants for the acid-catalyzed hydrolysis of glycosides and nucleosides are a function of both K_a and k_2,[2,20,21] the corresponding ρ_I values are the sum $\rho_{(K_a)} + \rho_{(k_2)}$. In this study, however, ρ_I is a function of only $\rho_{(k_2)}$. Therefore, in the absence of other factors, the observed ρ_I for acid-catalyzed hydrolyses should differ from the ρ_I for the corresponding pH-independent reaction by the value of $\rho_{(K_a)}$. Accurate quantitation of this distinction is not, however, possible at this time based on existing data from the literature.[22] Further structure–reactivity studies with other substituted nicotinamide nucleosides are underway and will be reported in subsequent publications.

Acknowledgment. This research was supported in part by National Institutes of Health Grant GM-22982.

Supplementary Material Available: Experimental procedures for hydrolysis and chromatography of the nicotinamide arabinoses (1 page). Ordering information is given on any current masthead page.

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(21) These authors have noted that substituent effects observed for 2-substituted glycoside hydrolysis must include the effects from the change in pK_a of the leaving group. However, no attempts were made to estimate the magnitude of the effect.
(22) The magnitude of the relative contributions of these two components for hydrolysis of 2-substituted-2′-deoxy-α-D-glycopyranosyl phosphates can be estimated from published data, albeit by a two-point analysis (2′-H vs 2′-F).[6] The $\rho_{(pK_a)}$ is −1.6 and the overall ρ_I for the reaction is −7.1, yielding a calculated $\rho_{(k_2)}$ of −5.5 for generation of a pyranosyl oxocarbocationic intermediate compared to the experimental value of −6.7 reported herein for furanosyls. Although the paucity of data prevents more detailed analyses, the ratio of $\rho_{(k_2)}$ to $\rho_{(K_a)}$ is 3.4 to 1, consistent with the diminution of inductive effects anticipated for a fully dissociative reaction, i.e., it follows the "rule of thirds" first proposed for substituent effects on the pK_as of aliphatic acids.[23] A value of $\rho_I = -8.7$ can also be calculated from a three-point analysis for the acid-catalyzed hydrolysis of 2-substituted (H, OH, or Cl) methyl β-D-glucopyranosides.[24]
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A Strategy for Synthesis of Conduritols and Related Cyclitols via Stereodivergent Vinylsilane–Aldehyde Cyclizations

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Summary: A novel stereospecific and stereodivergent cyclization of vinylsilane–aldehyde **10**, derived from L-arabinose, has been used to prepare the scalemic protected conduritols **11** and **12**.

The cyclitols[1] are a diverse class of compounds that have in common a polyhydroxylated cycloalkane moiety, with the cyclohexane skeleton being the one most often encountered. Their structural diversity is matched by their range of biological activity. Phosphorylated inositols, for instance, have been shown to be regulators of a number of cellular processes.[2] Aminodeoxyinositols and -conduritols (1,2,3,4-cyclohexenetetrols)[3] make up the aglycons of the aminocyclitol antibiotics.[4] A number of conduritol derivatives have been found to be glycosidase inhibitors,[3,5] as well as to possess antifeedant,[6] antibiotic, antileukemic, tumorostatic, and growth-regulating[3] activity.

The synthesis of both the parent conduritols and O-protected derivatives has been the focus of considerable synthetic effort. Previously, scalemic conduritols have been prepared from carbohydrates[6,7] via the Ferrier reaction,[8] from microbial oxidation products of substituted benzenes,[9] and by deoxygenation of chiral inositols.[10] We now report a novel method of cyclitol synthesis that is both

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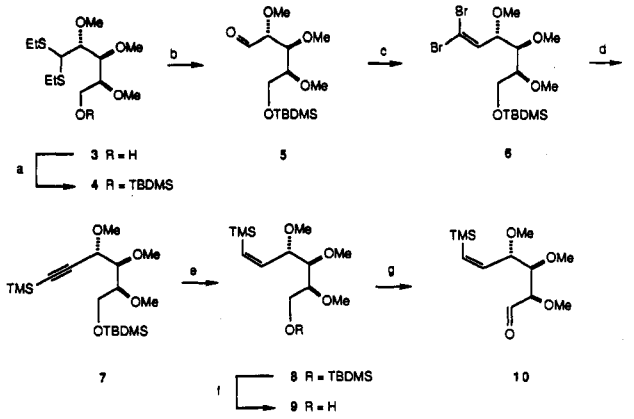
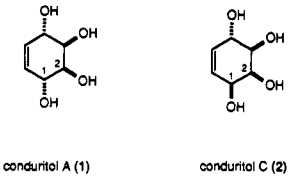
0022-3263/91/1956-5010$02.50/0

Scheme I[a]



[a] (a) TBDMSCl, imidazole, DMAP, DMF, rt, 12 h, 86%; (b) HgO, $HgCl_2$, acetone/water (9/1), 50–55 °C, 1 h, 98%; (c) KOtBu, PPh_3, $CHBr_3$, toluene, −20 °C–rt, 81%; (d) (i) n-BuLi, TMEDA, THF, −78 °C, (ii) TMSCl, −78 °C–rt, 73%; (e) $Pd/BaSO_4$, H_2, pyridine, rt, 20 h, 91%; (f) $HOAc/H_2O$ (2/1), 16 h, rt, 80%; (g) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, −78–0 °C, 98%.

stereospecific and stereodivergent, in which the cyclization of a sugar-derived vinylsilane–aldehyde is used to prepare a protected conduritol possessing either the 1,2-anti or 1,2-syn stereochemistry, as is found in conduritols A (1) or C (2), respectively.

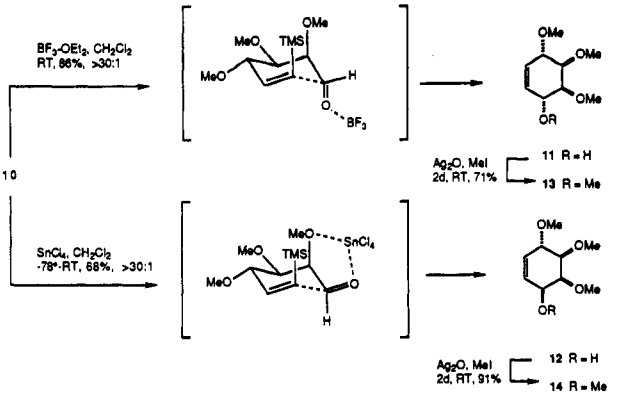


conduritol A (1) conduritol C (2)

Our synthesis of the key vinylsilane precursor **10** began with the known dithioacetal trimethyl ether **3**[11] (Scheme I), prepared in three steps from L-arabinose. Since the primary purpose of the work outlined here was to demonstrate the feasibility of the cyclization methodology, stable methyl ether protecting groups were used rather than a more easily removable group (e.g. MEM, MOM, etc.). The primary hydroxyl group of **3** was protected to give the TBDMS ether **4**, followed by removal of the dithioacetal function to yield aldehyde **5**. Wittig olefination[12] of **5** afforded the dibromide **6**, which was converted to the silylacetylene **7** using the Corey–Fuchs[13] protocol. Reduction of **7** to the vinylsilane **8** was accomplished by partial catalytic hydrogenation to produce an inseparable 20/1 mixture of *Z*/*E* isomers. Removal of the silyl ether protecting group[14] yielded alcohol **9**, which was oxidized to afford the desired aldehyde **10**.

In the pivotal cyclization step, treatment of vinylsilane–aldehyde **10** with $BF_3{\cdot}OEt_2$ at room temperature gave the 1,2-anti cyclohexenol **11** in 86% yield with >30:1 isomeric purity (Scheme II). By contrast, treatment of

Scheme II



10 with $SnCl_4$ at −78 °C, followed by warming to room temperature, gave the 1,2-syn cyclohexenol **12** in 68% yield, also with >30:1 isomeric purity.[15]

The cyclization of **10** to **11** presumably occurs via a chairlike transition state, with the BF_3-coordinated aldehyde oxygen assuming a pseudo-axial disposition to avoid a 1,2 steric interaction with the α-methoxy group, resulting in the 1,2-anti relationship (Scheme II). On the other hand, chelation-controlled cyclization of **10** to **12** using $SnCl_4$ enforces a pseudo-equatorial disposition of the aldehyde oxygen, resulting in the 1,2-syn stereochemistry.[16] The isomers **11** and **12** were readily distinguished and characterized by conversion to their respective tetramethyl ethers by treatment with Ag_2O in methyl iodide to give the known meso tetra-*O*-methylconduritol A (**13**) having spectra as reported[17] and the scalemic tetra-*O*-methylconduritol C (**14**), respectively.

Two novel features incorporated in the approach to cyclitols outlined above are (1) the first demonstration that a vinylsilane–aldehyde can be cyclized to give an allylic alcohol[18–20] and (2) the fact that an α-alkoxy group can

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(14) Tetrabutylammonium fluoride in THF at rt gave a significant amount of desilylation of the vinylsilane function. By contrast, treatment of silyl ether **9** with 2/1 $HOAc/H_2O$ at rt gave clean desilylation of the ether without protodesilylation of the vinylsilane.

(15) Cyclization of **10** to **11**: a solution of 1.1 equiv of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 was added over 30 min to aldehyde **10** at rt, which was followed by quenching of the reaction mixture with aqueous $NaHCO_3$. Significantly lower selectivity was observed in the cyclization when the $BF_3{\cdot}OEt_2$ was added rapidly to the reaction mixture. Cyclization of **10** to **12**: a solution of 2 equiv of $SnCl_4$ in CH_2Cl_2 was added to aldehyde **10** at −78 °C. After warming to rt, the reaction mixture was quenched with aqueous $NaHCO_3$. Ratios of the cyclization products were determined by ^1H NMR integration of the crude mixtures, which were then separated by preparative TLC for full characterization (see supplementary material).

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(17) Cambie, R. C.; Renner, N. D.; Rutledge, P. S.; Woodgate, P. D. *Synth. Commun.* **1989**, *19*, 537.

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(19) (a) Two examples of cyclizations of vinylsilanes with enals have been reported: Tius, M. A.; Ali, S. *J. Org. Chem.* **1982**, *47*, 3163. However, the isolated compounds were derived primarily from in situ aromatization of the initial cyclization products to give substituted biphenyls. (b) A single example of a vinylsilane cyclization with a ketone to give an allylic alcohol in modest yield has been reported: Hoflack, J.; De Clerq, P. J. *Bull. Soc. Chim. Belg.* **1983**, *92*, 407.

(20) (a) Fleming has reported the preparation of a methylcyclohexenyl ether by cyclization of an (*E*)- or (*Z*)-vinylsilane with an oxonium ion derived from a dimethyl acetal: Fleming, I.; Chow, H.-F. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1815. (b) Tius has reported a related cyclization (Tius, M. A. *Tetrahedron Lett.* **1981**, *22*, 3335), although the intermediate allylic ethers undergo in situ aromatization as in ref 19a to yield substituted biphenyls.

provide a critical element of 1,2-stereocontrol via Lewis acid complexation in these cyclizations. A variety of scalemic cyclitols could, in principle, be prepared from pentoses via our stereodivergent vinylsilane–aldehyde cyclization strategy.

Acknowledgment. This work was supported by the National Institutes of Health (CA-34303).

Supplementary Material Available: Experimental and spectral data for all new compounds, ^{13}C NMR spectra for compounds 5, 6, 7, 9, 10, 11, 12, 13, and 14, and ^{1}H NMR spectra for compounds 11 and 12 (15 pages). Ordering information is given on any current masthead page.

Articles

Relationships between the Aqueous Acidities of Some Carbon, Oxygen, and Nitrogen Acids and the Calculated Surface Local Ionization Energies of Their Conjugate Bases

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Average local ionization energies ($\bar{I}(\mathbf{r})$) have been computed on the molecular surfaces of the conjugate bases for four different groups of carbon and oxygen acids using an ab initio self-consistent-field molecular orbital approach. The lowest surface $\bar{I}(\mathbf{r})$ ($\bar{I}_{S,min}$) are generally found on the atom from which the proton has been abstracted. Good linear relationships between aqueous acidities and $\bar{I}_{S,min}$ are found for the different groups. A single linear relationship between pK_a and $\bar{I}_{S,min}$ that includes the four groups and three additional nitrogen acids also exists; the correlation coefficient is 0.97. This provides a means for predicting the pK_a's of a large variety of carbon, oxygen, and nitrogen acids.

Introduction

Acidity is a fundamental and very practical chemical concept. Although acidities have long been evaluated experimentally, their determination by computational techniques encounters significant problems.[1,2] Accurate calculation of gas-phase acidities requires the use of ab initio methods with large basis sets that include diffuse functions,[1,2] thus limiting the sizes of the systems that can be treated. The calculation of solution acidities is even more demanding since quantum chemical approaches must be supplemented by statistical mechanical considerations.[2]

We have recently shown, for a series of azines and azoles, that an excellent correlation exists between the lowest values of the average local ionization energies $\bar{I}(\mathbf{r})$, computed on their gas-phase three-dimensional molecular surfaces, and the aqueous solution acidities (pK_a's) of their conjugate acids.[3] In this study, we explore possible extensions of this relationship to other classes of acids. We show that there exist linear relationships between our calculated $\bar{I}(\mathbf{r})$ values and the experimentally determined pK_a's of the conjugate bases of a variety of carbon, nitrogen, and oxygen acids.

$\bar{I}(\mathbf{r})$ has recently been introduced as a useful property for studying molecular reactivity.[3-5] It is rigorously defined within the self-consistent-field molecular orbital (SCF-MO) framework by eq 1. $\rho_i(\mathbf{r})$ is the electronic

$$\bar{I}(\mathbf{r}) = -\sum_i \frac{\rho_i(\mathbf{r})\epsilon_i}{\rho(\mathbf{r})} \qquad (1)$$

density at the point $\mathbf{r}$ of the ith molecular orbital, having an orbital energy ϵ_i, and $\rho(\mathbf{r})$ is the total electronic density. According to Koopmans' theorem, the energy required to remove an electron can be approximated by the absolute value of its orbital energy.[6] $\bar{I}(\mathbf{r})$ can therefore be interpreted as the average energy required to remove an electron from any point $\mathbf{r}$ in the space of an atom or molecule. At those points where $\bar{I}(\mathbf{r})$ has its lowest values are to be

Table I. Experimentally Determined pK_a's and Calculated $\bar{I}_{S,min}$ for Some Substituted Methanes

conjugate base	conjugate acid pK_a[a]	$\bar{I}_{S,min}$ (eV) [6-31G*/3-21G]
CH_3^-	40.	0.101
CH_2CN^-	25.	2.906
$CH(CN)_2^-$	11.2	5.475
$CH_2NO_2^-$	10.2	5.630
$CHClNO_2^-$	7.2[b]	7.179
$CH(NO_2)_2^-$	3.6	7.622
$C(NO_2)_3^-$	0.1	8.917
$C(CN)_3^-$	-5.0[c]	7.712
$C(NO_2)_2CN^-$	-6.2	9.052

[a] Reference 12. [b] Reference 13. [c] Measured in aqueous sulphuric acid.[12]

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