Table II. Preparative Synthesis of Oligopeptides via Segment Condensation Catalyzed by Thermolysin in *tert*-Amyl Alcohol Containing 1% of Water and 9% of a Water Mimic[a]

COOH donor	NH_2 donor	reactn product[b]	isolated yield, %
Z-Gly-Gly-Phe	Phe-NH_2	Z-Gly-Gly-Phe-Phe-NH_2[c]	76
Z-Gly-Gly-Phe	Phe-Phe-NH_2	Z-Gly-Gly-Phe-Phe-Phe-NH_2[d]	72
Z-Gly-Pro-Phe-Pro-Leu	Leu-NH_2	Z-Gly-Pro-Phe-Pro-Leu-Leu-NH_2[e]	73
Z-Gly-Pro-Gly-Gly-Pro-Ala	Leu-Leu-Phe-NH_2	Z-Gly-Pro-Gly-Gly-Pro-Ala-Leu-Leu-Phe-NH_2[f]	67

[a] Conditions: 3 mg/mL thermolysin (prepared as described in footnote *a* to Table I) was used as a catalyst at 45 °C; water mimics were ethylene glycol in the fourth entry and formamide in all others; suspensions containing the enzyme and substrates were shaken at 300 rpm. The COOH and NH_2 donor substrate concentrations were, respectively, 150 and 200 mM (first entry), 40 and 50 mM (second entry), 100 and 200 mM (third entry), and 40 and 80 mM (fourth entry). The reaction times were (top to bottom) 17, 37, 30, and 96 h. The peptide synthesis reactions were stopped by evaporating the solvent under vacuum; the residues formed were washed with 1 N HCl, 0.5 M $NaHCO_3$, and water, followed by drying and recrystallization/reprecipitation. See footnote *c* to Table I for the meaning of "1% of water" here. Note that, apart from their enzyme activating effect, ethylene glycol and formamide greatly improve the solubility of peptides in *tert*-amyl alcohol. [b] Product compositions were confirmed by amino acid analysis. [c] The crystalline product (64 mg) had mp 201-202 °C and $[\alpha]^{25}_D$ -24.0° (*c* 0.2, DMF). [d] The amorphous product (61 mg) had $[\alpha]^{25}_D$ -18.0° (*c* 0.2, DMF). [e] The amorphous product (56 mg) had $[\alpha]^{25}_D$ -77.5° (*c* 0.2, DMF). [f] The amorphous product (65 mg) had $[\alpha]^{25}_D$ -59.5° (*c* 0.2, DMF).

h, when 82% of Z-Gly-Gly-Phe has reacted, almost one-third of the product is the dipeptide Z-Gly-Gly (with the rest being the desired tetrapeptide).[11]

In a quest to reconcile the opposing effects of water on the desired product yield and enzymatic reaction rate, we have addressed the latter phenomenon mechanistically. It seems likely that water activates thermolysin by enhancing the enzyme's conformational flexibility.[8,12] Since water's role as a molecular lubricant in proteins[13] is due to its ability to form multiple hydrogen bonds, other solvents mimicking water in this respect may, at least partially, substitute for it without promoting the hydrolytic side reactions. This hypothesis has been experimentally confirmed with several hydrogen bond forming solvents:[14] as seen in Table I, when three-quarters of the 4% of water in *tert*-amyl alcohol are replaced with 9% of formamide, the high level of thermolysin activity is retained, exceeding the rate observed when water is omitted by 200-fold; with two other water mimics,[14] ethylene glycol and glycerol, the reaction rates are not as high but still far greater than without them. Indicatively, the lesser the solvent's ability to form multiple hydrogen bonds, the lower its activating action on thermolysin (Table I).

Encouraged by the vigorous peptide synthesis catalyzed by thermolysin in *tert*-amyl alcohol containing 1% of water and 9% of formamide, we have utilized this solvent for the preparative enzymatic synthesis of Z-Gly-Gly-Phe-Phe-NH_2. As shown in the first line of Table II, the tetrapeptide has been prepared with a good yield; significantly, no formation of byproducts has been detected, in contrast to the situation observed at a 4% of water content.

The substrate specificity of thermolysin in *tert*-amyl alcohol containing either 1% of water and 9% of formamide or 4% of water is similar to that in water:[9] L-Phe and L-Ala are favored as carboxyl and L-Phe and L-Leu as amino group donors.[15] When thermolysin was presented with *N*-Ac-Phe and Phe-Lys-*O*-*tert*-Bu as substrates, only the natural Phe-Phe (as opposed to the unnatural Phe-ε-Lys) linkage was formed,[16] pointing to thermolysin's high fidelity even under these extreme conditions.

Table II depicts the results of the preparative segment condensation catalyzed by thermolysin in *tert*-amyl alcohol containing 1% of water and 9% of formamide or ethylene glycol. Four tetra- to nonapeptides were prepared in one step, with good isolated yields and with no appreciable secondary cleavage. Thus partial replacement of water with water-mimicking cosolvents may be beneficial for enzymatic peptide segment coupling by combining high reaction rates and the absence of side reactions. This approach should be applicable to other water-sensitive enzymatic processes in nonaqueous media.

Registry No. $CH_3CH_2CMe_2OH$, 75-85-4; Z-Gly-Gly-Phe, 13171-93-2; Phe-NH_2, 5241-58-7; Z-Gly-Pro-Phe-Pro-Leu-OH, 61867-13-8; Z-Gly-Pro-Gly-Gly-Pro-Ala-OH, 13075-38-2; Phe-Phe-NH_2, 15893-46-6; Leu-NH_2, 687-51-4; Leu-Leu-Phe-NH_2, 108370-29-2; Z-Gly-Gly-Phe-Phe-NH_2, 123963-61-1; Z-Gly-Gly-Phe-Phe-Phe-NH_2, 123963-62-2; Z-Gly-Pro-Phe-Pro-Leu-Leu-NH_2, 123992-45-0; Z-Gly-Pro-Gly-Gly-Pro-Ala-Leu-Leu-Phe-NH_2, 123963-63-3; H_2NCHO, 75-12-7; $HOCH_2CH_2OH$, 107-21-1; $(CH_2OH)_2CHOH$, 56-81-5; $MeOCH_2CH_2OH$, 109-86-4; MeOH, 67-56-1; $MeOCH_2CH_2OMe$, 110-71-4; Me_2NCHO, 68-12-2; thermolysin, 9073-78-3; tetrahydrofuran, 109-99-9.

(17) This work was financially supported by NIH Grant GM39794.

(11) Conditions: 20 mM Z-Gly-Gly-Phe, 50 mM Phe-NH_2, and 1 mg/mL thermolysin; for other conditions, see Table I. The enzymatic reaction was followed by HPLC precalibrated with the authentic peptides.

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(16) Determined by HPLC precalibrated with both isomers synthesized by the methods described in ref 10b and confirmed by ^1H NMR.

Substituent Effects on the Gas-Phase Acidity of Silane

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In a previous paper,[1] the gas-phase acidities of XH_n compounds (X = C, N, O, F, Si, P, S, Cl) were predicted with ab initio wave functions. At the MP4[2] level of theory with extended basis sets [6-311++G(3df,2pd)[3] for second-period atoms and 6-31++G(3df,2pd)[4] for third-period atoms], the calculated gas-phase acidities for these species were determined to be within 2 kcal/mol of experimental values. Similar results for the second period were obtained by DeFrees and McLean.[5]

In the present work, with 6-31G(d) geometries and full MP4/MC-311++G[6](3df,2pd) energies, the effects of CH_3, NH_2,

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Table I. Structural Features[a] for Neutral $XSiH_3$ and $XSiH_2^-$

	R(Si–X)		R(Si–H)		X–Si–H	
X	neutral	anion	neutral	anion	neutral	anion
CH_3	1.890	1.982	1.484	1.547	110.6	97.4
NH_2	1.730	1.842	1.480	1.544	108.2	97.9
			1.488	1.562	115.4	101.4
OH	1.653	1.754	1.483	1.561[b]	111.3	99.1[b]
			1.474	1.547[c]	106.7	100.0[c]
F	1.599	1.684	1.476	1.554	108.6	98.6
SiH_3	2.361	2.401	1.483	1.535	110.4	94.9
PH_2	2.271	2.366	1.480	1.533	108.0	93.9
			1.481	1.535	113.9	98.6
SH	2.156	2.310	1.478	1.533[b]	111.0	97.1[b]
			1.475	1.531[c]	105.1	95.8[c]
Cl	2.073	2.289	1.471	1.532	108.2	94.9

[a] Bond lengths in angstroms; angles in degrees; for X = NH_2 and PH_2, there are two distinct Si–H bonds. [b] Tent conformation. [c] Plow conformation.

OH, F, SiH_3, PH_2, SH, and Cl on the gas-phase acidity of silane are examined. Only a few related calculations have been carried out. Hopkinson and Lien,[7] using a double ζ (DZ) basis set and self-consistent field (SCF/DZ) wave functions, found that HCO and CN groups stabilize the SiH_3^- anion. Damewood and Haddad[8] determined that SiH_2X^- anions with X = H, SiH_3, HCO, and BH_2 are pyramidal, with the first three substituents giving large barriers to inversion. Magnusson[9] investigated the species SiH_3X and SiH_2X^- for X = BH_2, CH_3, NH_2, OH, F, with SCF/6–31G(d,p) wave functions at geometries determined with a smaller basis set.

All calculations were performed with GAUSSIAN86,[10] and all structures were verified as minima by diagonalizing the analytically determined hessians. The SCF/6–31G(d) vibrational frequencies were scaled by 0.89[11] to obtain corrected zero-point vibrational energies (ZPE). Only the valence electrons were correlated in the perturbation theory calculations.

The essential structural features of the parent neutral species and the corresponding anions are summarized in Table I. Note that two stable structural isomers, referred to as "tent" and "plow", were found for the X = OH and SH anions. These correspond, respectively, to structures in which the OH (SH) bond is eclipsed or staggered with the bisector of the opposing SiH_2 group. In both cases, the more open plow structure is found to be slightly lower in energy (see Table III). From Table I, three interesting structural features emerge: Upon deprotonation, the Si–X bond length increases. For the second-period substituents, this increase is nearly constant at about 0.1 Å. For third-period substituents, the increase appears to grow with the electronegativity of X, from 0.04 Å for X = SiH_3 to 0.21 Å for X = Cl. The increase in the Si–X bond length is accompanied by an increase in the remaining Si–H bond lengths of 0.06–0.08 Å and a decrease in the X–Si–H angle by 10–15°. Both of the latter two trends are probably related to the presence of a new lone pair adjacent to the remaining Si–H bonds and to the stretched Si–X bond.

The 6-31++G(d,p) energies are shown in Table II at the SCF, MP2, and MP4 levels. The SCF and MP2 energies for the extended basis set are shown in the same table. The corresponding gas-phase acidities, uncorrected for ZPE, are listed in Table III. Also listed in Table III are the 0 K MP2/MC-311++G(3df,2pd) enthalpy differences. On the basis of the results for the smaller basis set, it is estimated that the MP4 enthalpy differences with the larger basis set will be smaller than the corresponding MP2 values by 0.00–0.03 eV. The only exception to this trend is PH2, for which MP4 increases the computed value by 0.01 eV. Of the gas-phase acidities given in Table III, only that for methylsilane has been determined experimentally. Brauman and co-workers[12a] have found that value to be 378.3 kcal/mol, while Damrauer et al. have reported a value of 383 kcal/mol.[12b] The MP2/MC-311++G(3df,2pd) gas-phase acidity in Table III is 380.5 kcal/mol. Corrected as noted above for the MP4–MP2 energy difference, the estimated MP4 value is 380.1 kcal/mol. This is within the error limits of and is bracketed by the two experimental measurements, thereby providing us with some confidence in the predictions for the other compounds.[13]

The values in Table III may be compared with the experimental and calculated gas-phase acidities for the parent silane of 16.23 and 16.15 eV, respectively. Thus, the second-period substituents decrease the gas-phase acidity of silane, making it more difficult to remove a proton from the silicon, while the third-period substituents have the opposite effect. Thus, the larger, more polarizable third-period substituents are better able to stabilize the negative charge in the anion, whereas the second-period substituents stabilize the neutral parent more than the corresponding anion. Within the group of second-period substituents, the gas-phase acidities decrease in the order F > OH > CH_3 > NH_2, with the greatest effect occurring between F and OH. A similar trend was found by the SCF/6-31G(d,p) calculations of Magnusson.[9] Presumably, the more electronegative F is better able to stabilize the excess negative charge, despite the larger number of atoms in the other groups, and the general trend (except for methyl) parallels the increasing electron-withdrawing ability of the substituents. The trend for third-period substituents is similar although considerably attenuated. Experimentally, it has been observed that the XC–H gas-phase acidity decreases slightly as X changes from $P(CH_3)_2$ to SCH_3 to Cl.[14]

The results presented here may be compared with those found for second-period-substituent effects on the methane gas-phase acidity by Spitznagel et al.,[15] using MP2/6-31+G(d) energies at 4-31+G geometries. These authors found that CH_3 substitution decreases the gas-phase acidity, NH_2 has little effect, and OH

Table II. Total Energies (Hartrees)

	6-31++G(d,p)			MC-311++G(3df,2pd)	
compd	SCF	MP2	MP4	SCF	MP2
CH_3SiH_3	−330.282 57	−330.538 10	−330.581 34	−330.320 62	−330.639 43
$CH_3SiH_2^-$	−329.658 74	−329.918 95	−329.962 69	−329.693 43	−330.022 69
NH_2SiH_3	−346.299 81	−346.581 48	−346.617 70	−346.348 91	−346.702 52
$NH_2SiH_2^-$	−345.674 38	−345.962 32	−345.999 39	−345.718 66	−346.083 65
$OHSiH_3$	−366.145 15	−366.436 25	−366.466 35	−366.205 77	−366.583 89
$OHSiH_2^-$ (tent)	−365.525 20	−365.822 18	−365.853 20	−365.579 24	−365.967 78
$OHSiH_2^-$ (plow)	−365.524 65	−365.822 40	−364.853 38	−365.579 18	−365.968 36
$FSiH_3$	−390.157 85	−390.436 90	−390.463 66	−390.221 02	−390.605 09
$FSiH_2^-$	−389.547 99	−389.831 20	−389.859 15	−389.605 94	−389.999 35
SiH_3SiH_3	−581.315 35	−581.518 50	−581.566 52	−581.376 29	−581.631 31
$SiH_3SiH_2^-$	−580.720 36	−580.929 07	−580.977 03	−580.770 06	−581.046 84
PH_2SiH_3	−632.545 05	−632.763 57	−632.810 43	−632.601 08	−632.891 49
$PH_2SiH_2^-$	−631.949 09	−632.170 32	−632.216 89	−632.001 62	−632.301 99
$SHSiH_3$	−688.780 58	−689.008 55	−689.050 77	−688.842 07	−689.150 98
$SHSiH_2^-$ (tent)	−688.187 57	−688.416 25	−688.458 65	−688.243 56	−688.560 78
$SHSiH_2^-$ (plow)	−688.187 96	−688.416 96	−688.459 36	−688.244 14	−688.561 78
$ClSiH_3$	−750.189 08	−750.418 07	−750.454 78	−750.252 30	−750.569 68
$ClSiH_2^-$	−749.600 38	−749.828 32	−749.865 79	−749.656 59	−749.980 40

Table III. Relative Energies (Electronvolts) for $XSiH_3 \rightarrow XSiH_2^- + H^+$ [a]

X	6-31++G(d,p) SCF	6-31++G(d,p) MP2	6-31++G(d,p) MP4	MC-311++G-(3df,2pd) SCF	MC-311++G-(3df,2pd) MP2	ΔH [b]
CH_3	16.97	16.85	16.83	17.06	16.78	16.50
NH_2	17.02	16.85	16.82	17.15	16.84	16.56
OH (tent)	16.87	16.71	16.68	17.05	16.76	16.47
OH (plow)	16.88	16.70	16.68	17.05	16.75	16.47
F	16.59	16.48	16.45	16.74	16.48	16.21
SiH_3	16.19	16.04	16.04	16.25	15.90	15.70
PH_2	16.22	16.14	16.15	16.31	16.04	15.75
SH (tent)	16.13	16.12	16.11	16.28	16.06	15.77
SH (plow)	16.12	16.10	16.09	16.26	16.03	15.74
Cl	16.02	16.05	16.03	16.21	16.03	15.73

[a] At the 6-31G(d) geometries. [b] Corrected for zero-point vibrational energies, scaled by 0.89.

and F increase the acidity. The effects of the substituents *relative to each other* are similar to those found here, except that the effect of NH_2 and CH_3 are reversed.

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Synthesis of Aldose Sugars from Half-Protected Dialdehydes Using Rabbit Muscle Aldolase[1]

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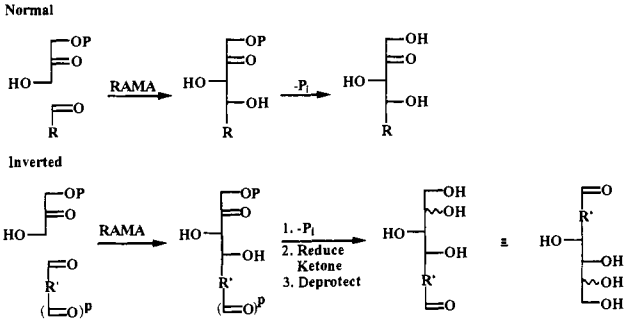
Rabbit muscle aldolase (RAMA) is a useful catalyst for the synthesis of sugars.[5,6] The "normal" application of this enzyme in synthesis is to catalyze the aldol condensation of dihydroxyacetone phosphate (DHAP) and an aldehyde with formation of a carbon–carbon bond having the D-threo configuration (Scheme I).[5]

Scheme I. Strategies for Using RAMA To Synthesize Ketoses and Aldoses[a]



[a] The designation $(=O)^p$ refers to a protected aldehyde group.

RAMA has three useful characteristics as a catalyst for aldol condensations: When RAMA is used, the hydroxyl groups present in the reactants need not be protected. It accepts a wide variety of aldehydes.[6] Its reactions are stereospecific. It also has limitations: It requires DHAP as one substrate, and it generates only vicinal diols having D-threo stereochemistry at C3–C4.[6] It also does not produce aldoses: Its products necessarily have a ketone group at C2 rather than an aldehyde group at C1. Conversion of a ketose to an aldose is not straightforward.[7]

Here we describe a new strategy for using RAMA (the "inverted" strategy, Scheme I) that increases the usefulness of this enzyme as a catalyst in the synthesis of sugars. We also demonstrate the value of L-iditol dehydrogenase (IDH) as a catalyst for the diastereospecific reduction of the ketone in this class of carbohydrates to an alcohol.[8,9]

RAMA-catalyzed aldol condensation between DHAP and a half-protected dialdehyde, $OCHR'(CHO)^p$, generates a protected aldose having a ketone (that derived from DHAP) at C_{n-1}. Dephosphorylation, reduction, or other transformation of the ketone and deprotection of the aldehyde provide the aldose. Both the structure of this aldose and the location of the vicinal diol formed in the aldol reaction can be controlled through the structure of R'. The ketone group derived from the DHAP offers control of the chemistry at the end of the sugar distal to the aldehyde. Scheme II illustrates this "inverted" approach to the synthesis of sugars using RAMA with syntheses of L-xylose (**4**) and 2-deoxy-D-*arabino*-hexose (**9**).

RAMA-catalyzed (50 units) condensation of diethoxyacetaldehyde (**1**)[10] (1 mmol, added in five portions over 5 days) and D-fructose 1,6-diphosphate (1 mmol) in the presence of triosephosphate isomerase (EC 5.3.1.1, ca. 200 units), followed by treatment in situ with acid phosphatase (AP, 20 units), afforded **2** in 60% overall yield.[11] Conversion of ketone **2** (1 mmol) to alcohol **3** with L stereochemistry was accomplished in 69% yield, using IDH (from *Candida utilis*, 10 units),[9] coupled with formate dehydrogenase (FDH, 10 units) and sodium formate (3 mmol)

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