yellow liquid: bp 118-122 °C (5.0 mmHg).

The product was deduced to be a 1:1 mixture of isomers by capillary GC and ^{1}H NMR analysis. No characterization data were reported for the individual components of this mixture in Danishefsky's original report.[4c]

4-Carbomethoxy-4-methylcyclohex-2-en-3-one. In a 10-mL round-bottomed flask, a solution of **3** (0.064 g, 0.235 mmol) and acetone (0.086 mL, 1.175 mmol) in 1 mL of methylene chloride was placed under argon and cooled to -78 °C. TMSOTf (0.19 mL of a 0.06 M methylene chloride solution, 0.0117 mmol) and collidine (0.078 mL of a 0.03 M methylene chloride solution, 0.0023 mmol) were combined in a 10-mL pear-shaped flask under argon and added to the adduct solution via a cannula, resulting in a clear straw-colored solution. After 5 min, the reaction was quenched with an additional 5 equiv of collidine in methylene chloride, poured into a separatory funnel containing 20 mL of cold 1 M pH 7.0 phosphate buffer, and extracted with three 10-mL portions of methylene chloride. The combined extracts were dried over sodium sulfate, filtered, and concentrated. Flash chromatography on 25 g of silica gel, using 20% ethyl acetate/hexanes as eluant, afforded 0.038 g (95.1% yield) of the enone as a clear, colorless liquid: R_f = 0.20 using 20% ethyl acetate/hexanes for development; ^{1}H NMR ($CDCl_3$) identical with published spectrum;[4c] ^{13}C NMR ($CDCl_3$) 24.4, 32.3, 34.2, 43.6, 52.1, 128.4, 151.2, 174.2, 197.6; IR (neat) 2960 (s), 1730 (s), 1680 (s), 1440 (s), 1260 (s), 1200 (s), 1120 (s); mass spectrum 168 (M^+), 140, 112, 109, 81; exact mass calcd for $C_9H_{12}O_3$ 168.0786, found 168.0777.

4-Carbomethoxy-3-methoxy-5-methyl-1-[(trimethylsilyl)oxy]cyclohex-1-ene (4). A solution of diene **1** (4.87 mL, 25.0 mmol) and methyl *trans*-crotonate (1.06 mL, 10.0 mmol) was heated in a heavy-walled glass tube at 120 °C for 30 h. Distillation[14] afforded 2.34 g (86.2% yield) of clear colorless liquid: bp 96-98 °C (0.4 mmHg).

The product was deduced to be a 2:1 mixture of isomers by capillary GC and ^{1}H NMR analysis. Danishefsky et al. obtained an identical ratio and determined the stereochemistry of the adducts by analysis of ^{1}H NMR coupling constants of the appropriate methine protons, although the NMR data were not reported.[4c]

4-Carbomethoxy-5-methylcyclohex-2-en-3-one. In a 10-mL round-bottomed flask, a solution of **4** (0.178 g, 0.652 mmol) and acetone (0.24 mL, 3.26 mmol) in 2 mL of methylene chloride was placed under argon and cooled to -78 °C. TMSOTf (0.54 mL of a 0.06 M methylene chloride solution, 0.032 mmol) and collidine (0.21 mL of a 0.03 M methylene chloride solution, 0.0063 mmol) were combined in a 10-mL pear-shaped flask under argon and then added to the adduct solution via a cannula, resulting in a clear, straw-colored solution. After 5 min, the reaction was quenched with an additional 5 equiv of collidine in methylene chloride and then poured into a separatory funnel containing 30 mL of cold 1 M pH 7.0 phosphate buffer and extracted with three 10-mL portions of methylene chloride. The combined extracts were dried over sodium sulfate, filtered, and concentrated. Acidic silica gel was prepared by stirring 240 g of silica gel with 300 mL of 2 M HCl for 30 min at room temperature. After the supernatant acid was decanted, the moist gel was dried in air at 25 °C overnight and then placed in an oven at 115 °C for 12 h. Flash chromatography on 13 g of this silica gel, using 27% ethyl acetate/hexanes as eluant (R_f = 0.25), afforded 0.101 g (92.8% yield) of a clear colorless liquid, shown to be a 27.5:1 mixture of double bond isomers **8** and **9** (uncorrected capillary GC). For **8**: ^{1}H NMR ($CDCl_3$) 1.03 (d, J = 6.1, 3 H), 2.10 (m, 1 H), 2.38-2.57 (m, 2 H), 3.40 (dt, J = 2.6, 9.0, 1 H), 3.69 (s, 3 H), 5.90 (dd, J = 10, 1 H), 6.79 (dd, J = 10, 1 H); ^{13}C NMR ($CDCl_3$) 19.8, 32.5, 44.4, 49.6, 52.1, 130.0, 145.3, 172.1, 197.8; IR (neat) 2960 (s), 1780 (s), 1710 (s), 1250 (s), 920 (s); mass spectrum 168 (M^+), 126, 109, 98, 81; exact mass calcd for $C_9H_{12}O_3$ 168.0786, found 168.0774.

5-Oxocyclohex-3-ene-1,2-dicarboxylic Acid Anhydride (2). A solution of **5** (0.439 g, 1.63 mmol) and acetone (0.60 mL, 8.15 mmol) in 1.5 mL of methylene chloride was placed under argon in a 25-mL round-bottomed flask and cooled to -78 °C. TMSOTf (1.35 mL of a 0.06 M methylene chloride solution, 0.08 mmol) was added via syringe. After 2 min, volatile materials were removed at -78 °C via vacuum (pump) through a needle. The remaining white solid was washed once with 5 mL of ice-cold 1:1 pentane/ethyl acetate and three times with 5-mL portions of ice-cold pentane. After each washing, the mixture was centrifuged and the supernatant removed via cannula. The remaining solvent was removed through a needle to afford 0.265 g (97% yield) of **2** as white crystals: mp 162-163 °C; ^{1}H NMR (acetone-d_6) 2.94 (m, 2 H), 3.34 (m, 2 H), 5.24 (dd, J = 2.0, 8.1, 1 H), 5.94 (ddd, J = 0.5, 2.8, 8.1, 1 H); ^{13}C NMR (acetone-d_6) 33.7, 39.3, 43.1, 132.5, 140.7, 170.2, 173.5, 193.4; IR (KBr) 3190 (m), 1780 (s), 1740 (s), 1240 (s); mass spectrum 166 (M^+), 138, 122, 94. Anal. Calcd for $C_8H_6O_4$: C, 57.84; H, 3.64. Found: C, 57.78; H, 3.66.

Acknowledgment. I wish to thank Dr. Robert Barkley for mass spectrometric analyses.

(14) Chromatographic purification of these and other adducts on silica gel resulted in the hydrolysis of a small fraction (<5%) of the adduct to methoxy ketone. The presence of any methoxy ketone complicated assessment of the subsequent TMSOTf reactions.

Hydrolysis of Dideoxygenated Purine Nucleosides: Effect of Modification of the Base Moiety[1]

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Dideoxynucleosides are receiving a considerable amount of interest currently because of their ability to inhibit the cytopathic effect of the human immunodeficiency virus (HIV-1), the etiologic agent of AIDS.[2-5] Dideoxyadenosine (ddA) and dideoxyinosine (ddI), members of this class of nucleosides, have potent activity against the AIDS virus and are currently undergoing extensive biological and clinical studies.[5-9] However, both ddA and ddI are unstable with respect to hydrolytic cleavage of the glycosidic bond.[10] This inherent factor limits considerably the usefulness of these compounds as biological probes and antiviral agents. The design of congeners that would be more stable hydrolytically than the parent compounds would be of considerable significance in this area. However, the rational design of such new analogues requires some information on the effect of structural modification on hydrolytic stabilities. Although the hydrolytic stabilities of ribonucleosides have received considerable attention,[11-15]

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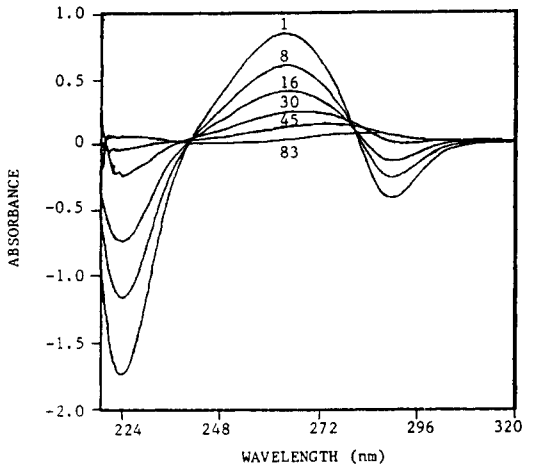


Figure 1. Differential UV spectra for the glycosidic bond hydrolysis of a representative compound, **12**, in 1×10^{-3} M HCl at 22 °C. Curves are labeled with respect to minutes of reaction.

the same cannot be said for dideoxynucleosides. We wish to report on the correlation of base structure and hydrolytic stability of some novel congeners of ddA.

Results and Discussion

Studies of the glycosidic bond hydrolysis of the dideoxynucleosides were carried out at pH 3 and 22 °C, where easily observable rates could be obtained. The reactions were followed by differential UV spectroscopy (Figure 1). Samples were monitored at appropriate time intervals by adjusting the pH to 13, thus separating the absorption of the unchanged nucleoside from that of the bathochromically shifted hydrolyzed base anion. For example, at pH 13, adenosine absorbs at 260 nm and adenine (as its anion) at 268 nm. The reference bases were synthesized in each case where they were unknown or not commercially available. The apparent first-order rate constants were calculated from the slopes of the log plots of eq 1 as described by Garrett and Mehta.[16] In this

$$\log (A - A_\infty) = \log (A_0 - A_\infty) - \frac{kt}{2.303} \qquad (1)$$

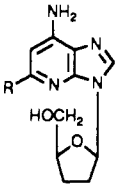
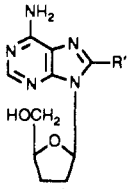
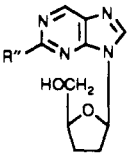
equation A = absorbance at time t, A_0 = initial absorbance, A_∞ = final absorbance, t = time, and k = apparent first-order rate constant. The relative rates of hydrolysis compared to ddA are summarized in Table I.

The acid-catalyzed glycosidic bond hydrolysis of purine nucleosides is believed to proceed by an A1 mechanism, the rate being dependent on the concentration of the protonated nucleoside.[12,14] Removal of the 2′-hydroxyl group and the 2′,3′-hydroxyl groups of adenosine dramatically enhances the rate of hydrolysis of the modified nucleosides,[10,16] presumably because of an increased tendency for the formation of an incipient carbonium ion at C-1′ because of the absence of the $-I$ effect of the hydroxyl group(s). Much less is known about the effect of modification of the base moiety.

Our data show that substitution at the 2-position, in general, results in decreased rates of hydrolysis. Thus, 2-amino, 2-cyano, 2-iodo, 2-(methylthio), 2-ethyl, and 2-(trifluoromethyl) analogues (compounds **2–7**) are all more stable than ddA. While the transposition of the amino group from the 6-position to the 2-position (compounds **1** and **14**) resulted in little change in the hydrolysis rate, replacement of the amino group with hydrogen (compound **13**) resulted in almost a 2-fold increase in the rate of hydrolysis. Although the pK_a data for protonation of N-1 varies considerably in the aforementioned compounds (see Table I), there appears to be no recognizable correlation between these pK_a values and the rates of hydrolysis.

The most dramatic effects of modification on hydrolysis rates occurred with the 8-position. While *O*-aralkyl, *S*-alkyl, and *O*-alkyl groups at this position increased the stabilities of these molecules (compounds **9**, **10**, and **11**), introduction of an NH_2 group at this position (compound **12**) decreased stability by a factor of 20. In stark contrast to this, when a hydroxyl group was introduced at the 8-position, the resulting compound (**8**, pK_a 3.2) was totally resistant to hydrolysis even at pH 1. As the rate of acid-catalyzed glycosidic bond hydrolysis is dependent to some extent on the concentration of the protonated nucleoside, the increased instability of the 8-amino compound **12** may be attributed to the marked resonance stabilization of the intermediate amidinium cation, which shifts the equilibrium of the initial protonation step toward this intermediate. Thus, it is possible that pK_{a_1} of this particular compound involves N-7 rather than N-1. The results with **8** are much more difficult to explain. Structurally this compound is different from the other dideoxynucleosides examined in that it exists almost entirely in the lactam form as evidenced from FTIR and high-field NMR data. A plausible explanation for the remarkable stability of **8** may be that facile hydrolysis requires the protonation of N-7, which is difficult in the inherent lactam form of **8** because of the weakly basic nature of this nitrogen (pK_a ~0, N-7). In contrast, and as supporting evidence for this

Table I. pK_{a_1} Data and Relative Rates of Hydrolysis of 2′,3′-Dideoxyadenosine Analogues at pH 3 and 22 °C

	compound	pK_a[a]	rel rate at pH 3[b]	λ (nm)[c]
	**1**, R = H	3.7	100	254.5
	2, R = NH_2	4.3	20	256.5
	3, R = CN	0.6	47	259
	4, R = I	1.4	55	259
	5, R = SCH_3	3.3	64	264
	6, R = CH_2CH_3	4.2	75	259
	7, R = CF_3	0.7	79	255
	**8**, R′ = OH	3.2	0[d]	
	9, R′ = OCH_2Ph	3.8	39	254.5
	10, R′ = SCH_3	3.6	40	269
	11, R′ = OCH_3	3.9	61	253
	12, R′ = NH_2	*e*	2050	263
	**13**, R″ = H	2.1	177	244.5
	14, R″ = NH_2	3.2	110	244.5

[a] Determined by UV spectrophotometric methods. [b] Rates of hydrolysis are relative to dideoxyadenosine (rate = 100). The apparent first-order rate constant for the hydrolysis of ddA at pH 3 is 8.23×10^{-4} min^{-1}. [c] Rate of change in absorbance monitored at this wavelength by differential UV spectroscopy. The monitoring wavelength represents the wavelength of maximum difference at pH 13 between the intact dideoxynucleoside and its cleaved heterocyclic base (see discussion above). [d] No detectable hydrolysis even at pH 1. [e] The pK_{a_1} of **12** could not be reliably determined because of its rapid breakdown under acidic conditions.

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explanation, protonation occurs readily for N-7 of 12. Further substantiating evidence for this comes from the observation that 7-deaza-2',3'-dideoxyguanosine is much more stable than 2',3'-dideoxyguanosine,[17] because of the absence of N-7 in the deaza compound.

In summary, while modifications at the 2- and 6-positions result in small but nevertheless significant effects on the rates of glycosidic bond cleavage of 2',3'-dideoxyadenosine analogues, the most dramatic effect is seen with appropriate substitution at the 8-position. These findings may be of significance in the design of stable biologically active dideoxynucleosides. They also contribute to further understanding of the mechanism of glycosidic bond hydrolysis of nucleosides.

Experimental Section

Synthesis. The compounds described in this project were synthesized by the dideoxygenation of the corresponding ribonucleosides using published procedures.[18,19] Functionalization of the ribonucleosides was carried out by thermal, photochemical, and metal-catalyzed methodologies previously described by us.[19-21]

Procedure for Kinetic Studies. Differential UV spectroscopy was used to observe the acid-catalyzed hydrolysis of the dideoxynucleosides.[16] Briefly, the dideoxynucleoside was dissolved in nitrogen-purged aqueous hydrochloric acid (pH 3) to give a 2.5×10^{-4} solution of the substrate. The solution was maintained at 22 °C and aliquots were removed periodically and adjusted to pH 13 with 0.25 M sodium hydroxide solution and monitored by UV spectroscopy. The blank was the appropriate base solution in each case of the same molarity as the initial dideoxynucleoside solution. The bases were prepared by the complete hydrolysis of the dideoxynucleosides. The differential UV spectra for the rate studies were recorded at periodic intervals between 200 and 320 nm on a Gilford Response spectrophotometer. The apparent first-order rate constants were determined from the slopes of the plots of absorbance versus time. These plots were generated by using TELEGRAF on a Prime 9950 computer.

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Synthesis and Characterization of the f(1.2) Molecular Fractal, 5,5-Bis(3',3'-dimethylbutyl)-2,2,8,8-tetramethylnonane

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A highly branched polymer molecule in which structures successively radiate from a central core has been described as an arborol,[1] a starburst polymer,[2] a dendrimer,[2c] a molecular fractal,[3] and a cascade molecule,[4] among others.

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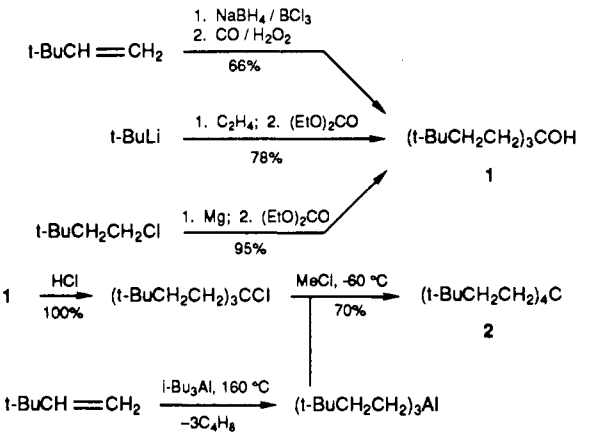
Table I. Heats of Vaporization[a]

compound	ΔH_v exp	ΔH_v calc: Trauton's law	ΔH_v calc: ref 8
n-$C_{16}H_{34}$	14.5,[b] 14.1[c]	12.3	18.6
2	14.0[b]	12.7	24.1

[a] All values in kilocalories/mole. Error estimated as ±0.5 kcal/mol. [b] This work. [c] Calculated from data in: Zwolinski, B. J.; Wilhoit, R. C. *Handbook of Vapor Pressures and Heats of Vaporization of Hydrocarbons and Related Compounds*; Thermodynamic Research Center, Department of Chemistry, Texas A & M University: College Station, TX, 1971; p K-5.

We describe the synthesis and characterization of an all-hydrocarbon representative f(1.2),[5] whose 36 equivalent external hydrogens comprise a prototype macromolecule with a uniform surface.

The compound of interest was prepared by three different methods, in order to find the best approach that might be directed toward the synthesis of still larger molecules of this type.



Compound 2 formed well-defined, hard crystals that showed no phase transitions in the DSC curve that would be indicative of plastic crystal behavior from room temperature to the melting point. The boiling point was difficult to measure in the conventional way because of the tendency of the compound to sublime, but values of 309-310 °C were obtained by a microprocedure,[6] in reasonable agreement with estimates from DSC curves (305-310 °C). The boiling point of 2 is over 100 °C lower than the extrapolated boiling point of the isomeric n-pentacosane (415 °C[7]), and this difference is consistent with the compact, globular structure of 2.

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