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Aromatic Nonpolar Nucleosides as Hydrophobic Isosteres of Pyrimidine and Purine Nucleosides

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Abstract

Described are the design, synthesis, and structures of three nonpolar nucleoside isosteres to be used as probes of noncovalent bonding in DNA and as isosteric replacements for the natural nucleosides in designed nucleic acid structures. Reaction of substituted aryl Grignards with 3',5'-bis-O-toluoyl- α -deoxyribofuranosyl chloride and subsequent deprotection with sodium methoxide in methanol afforded the two β -C-nucleoside pyrimidine analogs **1** and **2**. The dimethylindolyl nucleoside **3**, a purine isostere, was obtained by a nucleophilic displacement on α -chlorodeoxyribofuranose by the sodium salt of 4,6-dimethylindole, followed by deprotection. Regio- and stereochemistry of the products were established with NOE difference spectra and ^1H NMR splitting patterns. Analogs **1** and **2** are nonpolar isosteres of thymidine, and nucleoside **3** is an isostere of 2-aminodeoxyadenosine, the triply-bonded Watson–Crick partner of thymidine. Semiempirical AM1 calculations were carried out to provide bond length information to assess structural similarities between the isosteres and their natural counterparts.

Introduction

The importance of noncovalent bonding in the structure and function of biomolecules has long been recognized. There is a relative abundance of studies of noncovalent bonding in water using synthetic receptors, which can be viewed as model systems for larger and more complex biopolymers.¹ Most of these host–guest interactions are driven by solvophobic, Van der Waals or electrostatic interactions, since hydrogen bonds are very weak in the aqueous environment.² Nevertheless, it is clear that hydrogen bonding plays a significant role in the stability of the DNA double helix.³ It is perhaps surprising that relatively few studies exist on the strength and importance of hydrogen bonds in the context of actual well-defined DNA structures. In addition to hydrogen bonding, recent studies in model RNA helices⁴ have suggested that face-to-face stacking of the aromatic bases plays a significant, and perhaps dominant, role in the stability of duplex RNA. The origins of base stacking stability in nucleic acids are still controversial, and there is relatively little experimental data which might better define the phenomenon in DNA.⁵

Because nucleic acid bases are limited to four predominant structures and a few closely related analogs, there is a limited number of available probes which can be used to investigate the parameters which contribute to base pairing. We felt, therefore, that generating new analogs of the natural nucleosides might be valuable for investigating these parameters in the context of well-defined synthetic DNA duplexes. By designing analogs which retain the closest possible structural and steric relationship to the natural bases but are not likely to form hydrogen bonds, we felt that it would be possible to generate useful new data on the importance of hydrogen bonding and base stacking in DNA.

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We designed isosteres **1** and **2** as analogs of thymidine, and compound **3** as an analog of 2-aminodeoxyadenosine, its triple hydrogen bonding partner. Several principles were used in the design of the isosteres. The compounds are the closest possible steric mimics of the natural structures, and are also isoelectronic with them. Fluorine is the isosteric replacement for oxygen, C-H groups replace N-H groups, and -CH₃ replaces -NH₂. These replacements were intended to greatly limit or abolish the ability of these compounds to undergo hydrogen bonding as occurs naturally in DNA. It is hoped that- such nonpolar nucleosides will allow us to probe the relative contributions of hydrogen bonding and base stacking in the formation of stable DNA duplex structures.

In this report we describe the design and synthesis of isosteric analogs **1**, **2** and **3**. Semi-empirical **AM1** calculations are used to evaluate the structural similarity between the nucleoside analogs and the natural structures they are designed to mimic.

Results and Discussion

Design

Our aim in design of the nonpolar nucleosides was to create the closest possible steric and structural mimics of the natural nucleosides which have limited potential for hydrogen bonding. Fluorine appeared to be one of the best possible substitutions for carbonyl-type oxygen both structurally and electronically, and although aromatic-substituted fluorine atoms can participate in weak intramolecular hydrogen bonds,⁶ NMR titration experiments with 2,4-difluorotoluene (the aromatic group of compound **1**) do not show any evidence of hydrogen bonding with potentially complementary partners.⁷ The aromatic C-F bond has similar polar qualities as the C=O bond, but considerably smaller in magnitude. For an even less polar version of thymine (compound **2**), we chose the methyl group as a replacement for oxygen, using a 1,2,4-substituted trimethylbenzene as the base isostere. This is a less conservative steric replacement, since the methyl groups are significantly larger than oxygen (see Figure 2). Finally, as a complement to the pyrimidine analogs we chose the purine analog 4,6-dimethylindole, a nonpolar steric mimic of 2-aminodeoxyadenosine, in which the two amino groups were replaced with methyl groups and the N-1, N-3, and N-7 groups were replaced with sp² hybridized C-H groups. In making this last substitution (CH for N:) there is again some increase in steric bulk, with protons occupying a greater volume than the nitrogen lone pairs; however, this is the closest possible steric substitution which can reasonably be accomplished.

The lack of polar functionality in these new analogs is expected to make them considerably more hydrophobic (less hydrophilic) than the natural nucleosides, and to greatly limit their hydrogen bonding capability. A few published examples exist in which researchers have examined bases with diminished H-bonding abilities.^{8,9} These studies were primarily aimed at design of a “universal” base with non-discriminatory base pairing properties for use in oligonucleotide sequencing probes and primers,^{8a} or as nucleosides for testing the pairing requirements of DNA polymerases.^{8b} To our knowledge none of the nucleosides in those studies had a complete absence of H-bonding groups. In addition, the focus of previous reports has been on pairing properties with natural bases, and no studies have been carried out to evaluate separately the H-bonding and base stacking properties of the analogs. Reports of other substituted phenyl ribosides exist in the literature;^{10,11} however, with one exception,¹² studies

of their pairing abilities were not undertaken. Finally, there is one recent report of a thiomethyl-substituted indole nucleoside to be used for disulfide crosslinking in synthetic oligonucleotides.¹³

Synthesis

Our strategy for formation of the glycosidic bonds for the C-nucleoside analogs relied on coupling of aryl Grignards with an α -chloro-substituted deoxyribose derivative.¹⁴ We used bromoaryl precursors for generation of the organomagnesium derivatives. There are two potential sites for bromination of 2,4-difluorotoluene; however, we found that the bromination occurred exclusively at the 5 position. The reaction proceeded most efficiently when it was performed with 2,4-difluorotoluene as the solvent. This procedure yielded the desired bromoaryl compound which needed no further purification.

Nuclear Overhauser enhancement studies were performed both on the starting 2,4-difluorotoluene and the brominated product to establish that we had indeed formed the 5-bromo-2,4-ditoluene rather than the 6-bromo isomer. Selective irradiation of the methyl group in the starting material gave enhancement of only the adjacent proton (Table 1). The same result was seen upon irradiation of the methyl group in the product. The complementary experiment in which we irradiated the proton at position 6 and looked for enhancement at the neighboring methyl group gave similar enhancements both in starting material and product (Table 1).

The first use of a Grignard reagent in the coupling of an aromatic hydrocarbon to a glycosyl chloride was report by Hurd and Bonner.¹⁵ Subsequent attempts at coupling of a Grignard reagent with a glycosyl halide by other groups proved futile,¹⁶ but fortunately this procedure provided us with our product **7** (Scheme 1), albeit in lower yields than reported by Hurd and Bonner. The low yield appeared to be due, at least in part, to α , β -elimination of the chloride under the basic reaction conditions, and to a smaller extent, reaction of the Grignard reagent with the protecting group esters. Attempts to increase the yield with larger ratios of Grignard reagent to sugar were unsuccessful. This type of glycosylation reaction has in general resulted in modest yields in previous literature reports. For example, Fox and coworkers used diphenylcadmium with the benzoyleated ribofuranosyl chloride to give the protected β -D-ribofuranosylbenzene in 20% yield.¹⁰ Millican and coworkers used coupling of phenylmagnesium bromide with the hemiacetal of 2'-deoxyribofuranose to give both α and β anomers with an overall yield of 21% of the β anomer.¹² In the present case, since the synthesis is short we were able to obtain readily the required amounts of product, and deprotection of the bistoluoyl intermediate with sodium methoxide in methanol afforded the nucleoside analog **1** in 80% yield.

The stereochemistry about the anomeric position was established by comparison of the splitting pattern of the anomeric proton in the ¹H NMR spectrum to similar compounds with the β configuration. The anomeric proton of β anomers gives a characteristic pseudo triplet while the anomeric proton of the alpha anomer gives a quartet.¹⁶ The splitting patterns and chemical shifts for the nucleosides **1–3** are shown in Table 2; we find that all three of the new nucleosides give the characteristic β -type splitting pattern. The isolation of the β -anomer as the primary product is also consistent with expectation that S_N2 attack of the Grignard reagent on the α -chloro-substituted anomeric carbon would give predominantly β -substituted product.

The synthesis of analog **2** followed the same procedure as the synthesis of **1** with one less step since 5-bromo-1,2,4-trimethylbenzene was commercially available. Treatment of 3',5'-di-O-toluoyldeoxyribofuranosyl chloride with 1,2,4-trimethylphenylmagnesiumbromide gave **8** in 22% yield. Deprotection of **8** with sodium methoxide in methanol gave, in quantitative yield, nucleoside isostere **2**.

We synthesized the 4,6-dimethylindole nucleoside **3** as a nonpolar purine analog and as a potential “pairing” partner for pyrimidine analogs **1** and **2**. There has been recent interest in indole-substituted nucleosides as potential purine surrogates.¹³ We used Nordlander’s synthesis of 4,6-dimethylindole from N-(trifluoroacetyl)-2-anilino acetal¹⁷ to obtain this base analog. This is a very efficient synthesis and after three steps provided us with 4,6-dimethylindole in an overall isolated yield of 74%. We used the method developed by Robins¹⁸ to couple the indole sodium salt to the ribofuranosyl moiety to obtain the N-glycosylated β -anomer (Scheme 2). Deprotection with sodium methoxide in methanol was performed as for **7** and **8** to give **3** (Table 2).

Structural Analysis

In designing the nucleoside analogs **1–3** we tried to deviate as little as possible from the steric shape and size of the natural bases, so that when incorporated into DNA the synthetic analogs would be less likely to disrupt the geometry of the DNA helix. Figure 2 shows calculated bond lengths obtained from AM1 semiempirical models of the aromatic portions of all three analogs and the two natural nucleosides. For easier visual comparison we have also included MM2-minimized space-filling CPK models for these structures.

The calculations indicate that difluoro-substituted thymidine analog **1** is a nearly perfect steric mimic for the natural thymidine structure. In particular, the carbon-fluorine bond lengths are within 0.1 Å of the C=O bonds they replace. Interestingly, data on the atomic charges (not shown) indicate that this analog has the same absolute signs for the charges on every atom as compared to thymine, although they are smaller in magnitude. Thus, compound **1** may be seen as a less-polarized version of thymidine. With the larger methyl groups substituting for oxygens, compound **2** is, of course, not as close a steric mimic for thymidine. It is of special interest because it is essentially a non-polarized version of compound **1**. Finally, compound **3** is a reasonably good steric mimic for 2-aminodeoxyadenosine; the methyl groups have somewhat greater diameter (especially out of the aromatic plane) than amino groups; in addition, three C-H groups replace aromatic ring nitrogens, and the protons have somewhat larger steric size than the nitrogen lone pairs they replace. Taken together, the three analogs, while not perfect steric mimics, are as close as can reasonably be achieved, and they are even iso-electronic with the natural structures.

A check on the reliability of the AM1 calculations is available by comparison with published high-resolution crystal structures for the natural bases. Comparison of the AM1 calculated bond lengths with bond lengths obtained from crystal structures of thymidine and adenosine¹⁹ shows that the AM1-derived values are accurate to within $\pm 2\%$. In addition, although crystal structures of our analogs are not available, data for aromatic C-F bonds in other systems²⁰ shows good agreement with our calculated values.

Conclusions

We have successfully synthesized three new hydrophobic isosteres of pyrimidines and purine nucleosides, using displacement reactions on an α -chloro-substituted deoxyribose derivative to direct anomeric stereochemistry. Semiempirical calculations of the structures indicate that they are close steric mimics of their natural thymidine and 2-aminodeoxyadenosine counterparts. Initial biophysical studies in the DNA context, now underway in our laboratory, have shown that these nucleosides possess some unusual noncovalent bonding characteristics and may aid in understanding the interactions important in the stabilization of DNA helices. Also under study are the noncovalent interactions of these and related nucleosides with proteins.

Experimental Section

General Remark

^1H NMR and ^{13}C spectra were obtained with a 300 MHz instrument, and chemical shifts are reported in ppm on the δ scale with the solvent as an internal reference. J values are given in Hz. NOE difference spectra were also performed on a 300 MHz instrument. Column chromatography separations were performed with EM Science Silica Gel 60, 230–400 mesh. Mass spectral analyses were performed by the University of Nebraska Mass Spectrometry Facility, Lincoln, NE.

Tetrahydrofuran and acetonitrile were distilled from calcium hydride. 1,2,4-Trimethylbenzene and 2,4-difluorotoluene were purchased from Aldrich. All other solvents and reagents were purchased from Aldrich, Sigma, J. T. Baker, or Fisher, and were used without further purification.

Semiempirical AM1 calculations²¹ were performed using the Mopac v6.0 package (J. J. P. Stewart, Quantum Chemistry Program Exchange, Dept. of Chemistry, Indiana University, Bloomington, IN)

5-Bromo-2,4-difluorotoluene (5)

2,4-Difluorotoluene (5.0 g, 39.0 mmol) was placed in a two-necked round bottomed flask equipped with an addition funnel and a condenser, with a drying tube filled with potassium hydroxide. Iron filings (100 mg) were added and the solution was heated to 60°C. Bromine (3.1 g, 39.0 mmol) was placed in the addition funnel and added to the 60°C solution dropwise over a period of one hour. The reaction was allowed to stir in the dark for an additional hour. The solution was poured into vigorously stirred 10% aqueous sodium hydroxide. The organic layer was collected and the aqueous layer extracted twice with benzene. The combined organic layers were washed with anhydrous sodium sulfate. The solution was concentrated to give a pale yellow liquid as product. No further purification was needed: ^1H NMR (CDCl_3 , ppm) 7.38 (1H, t, $J=8$), 6.85 (1H, t, $J=10$), 2.24 (3H, s); ^{13}C (CDCl_3 , ppm) 8.7, 97.8 (dd), 99.5 (t), 117.3 (dd), 129.5 (d), 153.5 (dd); HREI calcd for $\text{C}_7\text{H}_5^{79}\text{BrF}_2$ 205.9542, found 205.9538; calcd for $\text{C}_7\text{H}_5^{81}\text{BrF}_2$ 207.9523, found 207.9518.

1',2'-Dideoxy-1'-(2,4-difluorotoluy)-3',5'-di-O-toluo-yl- β -D-ribofuranose (7)

Dry THF (5.0 mL) was placed in a round-bottomed flask equipped with a condenser, drying tube and addition funnel. Magnesium turnings (0.24 g, 10.0 mmol) and a few crystals of iodine were added. 5-Bromo-2,4-difluorotoluene (2.1 g, 10.0 mmol) (**5**) was added dropwise to the mixture. Slight heating was needed (40°C) to drive the reaction to completion. After formation of the Grignard reagent was complete (~1 h) 1'- α -chloro-3',5'-di-O-toluo-yl-2'-deoxyribose¹⁴ (2.98 g, 7.4 mmol) dissolved in THF was added dropwise via an addition funnel over a period of 1 h. The solution was stirred at room temperature overnight under an atmosphere of nitrogen. The solution was then poured into 10% ammonium chloride (75 mL) and extracted with methylene chloride. The organic layer was washed with saturated sodium bicarbonate and brine and dried over anhydrous sodium sulfate. The solution was filtered, concentrated and purified by silica gel chromatography eluting with hexanes-ethyl acetate (80:20). The product was obtained as a pale yellow oil in 23% yield (800 mg, 1.70 mmol). R_f : 0.45 (ethyl acetate: hexanes, 20:80): ^1H NMR (CDCl_3 , ppm) 7.98 (2H, d, $J=8$), 7.69 (2H, d, $J=8$), 7.41 (1H, t, $J=8$), 7.27 (2H, d, $J=8$), 7.19 (2H, d, $J=8$), 6.76 (1H, t, $J=10$), 5.61 (1H, br s), 5.57 (1H, t, $J=6'$), 4.74 (1H, br s), 4.57 (2H, t, $J=5$), 3.02–2.93 (1H, m), 2.43 (3H, s), 2.41 (3H, s), 2.23 (3H, s); ^{13}C NMR (CDCl_3 , ppm) 14.0 (d), 21.6, 39.4, 64.5, 74.8, 76.3, 82.5, 103.1 (t), 120.1 (dd), 125.2 (dd), 126.5, 126.8, 128.8, 128.9, 129.3, 129.5, 143.6, 143.8, 158.6 (dd), 165.6, 166.0; HRFAB (3-NBA matrix) calcd for $\text{C}_{28}\text{H}_{26}\text{F}_2\text{O}_5\text{Na}$ 503.1646, found 503.1636.

1',2'-Dideoxy-1'-(2,4-difluorotoluoyl)- β -D-ribofuranose (1)

The diester (**7**) (800 mg, 1.70 mmol) was dissolved in 10 mL methanol containing 40 mg sodium methoxide and stirred for 3 h. Solid ammonium chloride was added until the pH was 8. The solution was then concentrated and purified by silica gel chromatography eluting with ethyl acetate:hexanes (60:40). The product was obtained as a clear oil in 92% yield (380 mg, 1.56 mmol). R_f : 0.13 (ethyl acetate: hexanes, 60:40); ^1H NMR (CDCl_3 , ppm) 7.37 (1H, t, $J = 8$), 6.74 (1H, t, $J = 10$), 5.27 (1H, t, $J = 6$), 4.46 (1H, q, $J = 7$), 4.10 (1H, q, $J = 7$), 3.89–3.74 (2H, m), 2.78–2.70 (1H, m), 2.25 (3H, s), 2.03–1.92 (1H, m); ^{13}C (CDCl_3 , ppm) 13.6 (d), 41.7, 61.9, 72.1, 73.3, 84.7, 102.9 (t), 120.2 (dd), 124.5 (dd), 128.6 (t), 158.6 (dd); HRFAB (3-NBA matrix) calcd for $\text{C}_{12}\text{H}_{14}\text{F}_2\text{O}_3\text{Na}$ 267.0809, found 267.0812.

1',2'-Dideoxy-1'-(1,2,4-trimethylphenyl)-3',5'-di-O-toluoyl- β -D-ribofuranose(8)

Grignard formation and subsequent coupling with the chlorosugar was performed in a manner similar to that for formation of compound **7**. 5-Bromo-1,2,4-trimethylbenzene (**6**) (1.2 g, 6.0 mmol) was coupled with 1'-chloro-3',5'-di-O-toluoyl-2'-deoxyribose¹⁴ (2.0 g, 5.0 mmol) in THF, which after purification by silica gel chromatography (CH_2Cl_2), gave the diester **8** in 22% yield. R_f : 0.21 (CH_2Cl_2); ^1H NMR (CDCl_3 , ppm) 8.02 (2H, d, $J = 8$), 7.86 (1H, d, $J = 8$), 7.45 (1H, s), 7.23–7.28 (5H, m), 6.95 (1H, s), 5.69 (1H, br s), 5.54 (1H, t, $J = 6$), 4.81 (1H, br s), 4.69–4.56 (2H, m), 3.07–2.98 (1H, m), 2.43 (6H, s), 1.35 (3H, s); ^{13}C (CDCl_3 , ppm) 18.3, 19.0, 19.1, 21.4, 39.1, 64.4, 76.3, 77.2, 81.6, 125.9, 126.7, 126.8, 128.8, 128.9, 129.5, 131.1, 131.5, 133.7, 135.0, 137.3, 143.5, 143.6, 165.9, 166.1; FAB (3-NBA matrix) ($\text{M}+\text{H}$)⁺ calcd for $\text{C}_{20}\text{H}_{32}\text{O}_5$ 473.3, found 473.5.

1',2'-Dideoxy-1'-(1,2,4-trimethylphenyl)- β -D-ribofuranose (2)

The diester (**8**) (480 mg, 1.01 mmol) was suspended in 6 mL of methanol containing 24 mg sodium methoxide, gently heated (40 °C) until all of the solid dissolved, and was then stirred at room temperature for an additional 2 h. Solid ammonium chloride was added to adjust the pH to 8. The solution was concentrated and the residue purified by silica gel chromatography (ethyl acetate:hexanes, 85:15) to give **2** (240 mg, 1.01 mmol) as a white solid in 100% yield. R_f : 0.28 (ethyl acetate:hexanes, 85:15); ^1H NMR (CDCl_3 , ppm) 7.33 (1H, s), 6.93 (1H, s), 5.26 (1H, t, $J = 6$), 4.47 (1H, br s), 4.16 (1H, br s), 3.99–3.76 (2H, m), 2.75–2.66 (1H, m), 2.29 (6H, s), 2.25 (3H, s); ^{13}C (CDCl_3 , ppm) 18.3, 19.0, 19.2, 41.9, 62.1, 72.4, 76.5, 84.6, 125.7, 125.8, 131.2, 131.5, 134.0, 135.1, 137.5; HRFAB (gly/3-NBA/TFA matrix) ($\text{M}+\text{H}$)⁺ calcd for $\text{C}_{14}\text{H}_{20}\text{O}_3$ 237.1491, found 237.1484.

1',2'-Dideoxy-1'-(4,6-dimethylindolyl)-3',5'-di-O-toluoyl- β -D-ribofuranose (10)

This compound was synthesized in a manner similar to that reported by Robins.¹⁸ The dimethylindole **917** was dissolved in dry acetonitrile and cooled to 0 °C. To this was added NaH (0.21 g, 8.9 mmol). After stirring for 30 min 1'-chloro-3',5'-di-O-toluoyl-2'-deoxyribose¹⁴ (2.3 g, 5.9 mmol) was added. After stirring under an atmosphere of nitrogen overnight the mixture was filtered and concentrated to give a brown residue. The residue was purified by silica gel chromatography (CH_2Cl_2) to give **10** as a yellow solid in 27% yield (800 mg, 1.6 mmol). R_f : 0.35 (CH_2Cl_2); ^1H NMR (CDCl_3 , ppm) 8.02 (2H, d, $J = 8$), 7.97 (2H, d, $J = 8$), 7.33 (2H, d, $J = 8$), 7.27 (2H, d, $J = 8$), 7.25 (2H, s), 7.2 (H2 obscured), 7.17 (1H, s), 6.81 (1H, s), 6.54 (1H, br s), 6.49 (1H, t, $J = 6$), 5.75 (1H, br s), 4.65 (2H, br s), 4.60 (1H, br s), 2.96–2.86 (1H, m), 2.74–2.66 (1H, m), 2.52 (3H, s), 2.48 (3H, s), 2.45 (3H, s), 2.42 (3H, s); ^{13}C (CDCl_3 , ppm) 18.3, 21.4, 37.5, 64.2, 74.9, 81.2, 85.2, 101.8, 107.1, 122.1, 122.2, 126.4, 126.5, 126.7, 128.9, 129.0, 129.4, 129.5, 129.9, 132.0, 136.0, 143.7, 144.1, 165.7, 166.0; HRFAB (3-NBA matrix) calcd for $\text{C}_{31}\text{H}_{31}\text{NO}_5$ 497.2202, found 497.2199.

1',2'-Dideoxy-1'-(4,6-dimethylindolyl)- β -D-ribofuranose (3)

The deprotection of diester **10** (750 mg, 1.51 mmol) was performed in a manner similar to that of compounds **7** and **8** above. Purification by silica gel chromatography ($\text{CH}_2\text{Cl}_2\text{:MeOH}$, 90:10) gave the product **3** in 89% yield (350 mg, 1.34 mmol). *R_f*: 0.40 ($\text{CH}_2\text{Cl}_2\text{:MeOH}$, 90:10): ^1H NMR (CDCl_3 , ppm) 7.19 (1H, d, $J = 3$), 7.16 (1H, s), 6.82 (1H, s), 6.56 (1H, d, $J = 3$), 6.40 (1H, t, $J = 6$), 4.66 (1H, br s), 4.03 (1H, q, $J = 4$), 3.86–3.72 (2H, m), 2.74–2.65 (1H, m), 2.53 (3H, s), 2.48 (3H, s), 2.46–2.40 (1H, m), 1.84 (br s), 2.06 (br s); ^{13}C NMR (CDCl_3 , ppm) 18.2, 21.5, 39.6, 62.2, 71.5, 84.2, 85.5, 101.6, 107.1, 122.2, 129.8, 132.0, 136.3; HRFAB (gly/3-NBA/TFA matrix) ($\text{M}+\text{H}$) $^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3$ 262.1443, found 262.1447.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Structures of the natural DNA nucleosides and of four proposed nonpolar isosteric analogs. The synthesis and structures of the thymidine and deoxyadenosine analogs (**1**, **3**) are described in this report.

Figure 2. Structural analysis for thymine, adenine, and the aromatic “bases” of analogs **1**, **2** and **3**. Shown are AM1 calculations of bond lengths and MM2-minimized structures displayed as space-filling CPK models.

Scheme 1.

Scheme 2.

Table 1¹H-NOE Data for Compounds 4 and 5

<div><div>4</div><div>Br₂/Fe</div><div>→</div><div>5</div></div>			
compd	signal irradiated	obsd NOE	%
4	CH ₃	H-5	2.2
		H-5	<0.2 ^a
	H-6	CH ₃	6.9
	H-5 ^b	<i>b</i>	<i>b</i>
5	CH ₃	H-6	3.4
	H-6	CH ₃	7.8

^aNo detectable signal intensity enhancement.^bCould not be selectively irradiated due to overlapping H-2 signal.

Table 2

¹H NMR Data for Nucleosides 1, 2, and 3 in CDCl₃

compd	chemical shifts for numbered positions ^a											
	1	2	3	4	5	6	7	1'	2'	3'	4'	5'
1	2.25 s		6.74 t			7.35 t		5.27 t	2.69–2.78 m, 1.95–2.04 m	4.46 q	4.10 q	3.72–3.86 m
2	2.24 s	2.24 s	6.92 s	2.29 s		7.31 s		5.22 t	2.62–2.72 m, 1.88–1.98 m	4.42 q	4.12 q	3.73–3.88 m
3		7.19 d	6.56 d	2.53 s	6.82 s	2.48 s	7.16 s	6.40 t	2.65–2.74 m, 2.40–2.46 ^b	4.66 broad s	4.02q	3.72–3.86 m

^aChemical shifts are reported in ppm and were obtained on a 300 MHz instrument. Symbols are defined as follows: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

^bPattern was obscured by the methyl singlet.