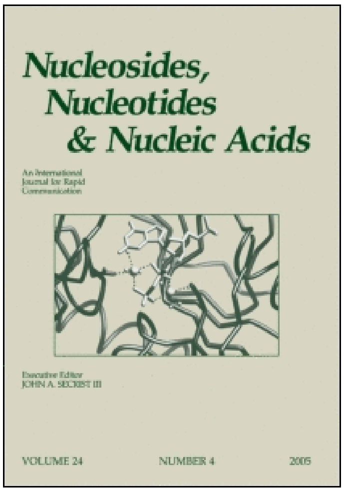

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PROSIT, an Online Service to Calculate Pseudorotational Parameters of Nucleosides and Nucleotides

Guangyu Sun[a]; Johannes H. Voigt[ab]; Victor E. Marquez[a]; Marc C. Nicklaus[a]
[a] Laboratory of Medicinal Chemistry, NCI—Frederick, CCR, NCI, NIH, DHHS, Frederick, Maryland, USA [b] Schering-Plough Research Institute, Kenilworth, NJ

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PROSIT, AN ONLINE SERVICE TO CALCULATE PSEUDOROTATIONAL PARAMETERS OF NUCLEOSIDES AND NUCLEOTIDES

Guangyu Sun, Johannes H. Voigt, Victor E. Marquez, and Marc C. Nicklaus
□ *Laboratory of Medicinal Chemistry, NCI—Frederick, CCR, NCI, NIH, DHHS, Frederick, Maryland, USA*

□ *The online service PROSIT (Pseudo-Rotational Online Service and Interactive Tool) is a free service available at http://cactus.nci.nih.gov/prosit/ that performs pseudorotational analysis of nucleosides(tides). PROSIT reads the 3D coordinates of nucleosides and returns the pseudorotational phase angle P, puckering amplitude* ν_{max}, *and other related information. As examples, the sugar conformations in a parallel-stranded guanine tetraplex and a four-way Holliday junction are presented here.*

INTRODUCTION

The sugar conformation in nucleosides and nucleotides plays an important role in defining their overall structures. Recent studies have shown that some nucleoside(tide) targeting enzymes preferentially bind to compounds with the furanose ring in a specific well-defined shape.[1–4] The shape of a nucleoside(tide) is defined by four conformational parameters:[5,6] the glycosyl torsion angle χ, the torsion angle γ, the phase angle P, and puckering amplitude ν_{max}; the latter two describing the sugar pucker and the degree of non-planarity of the pentofuranose ring. The combination of P and ν_{max} simplifies the description of the rather complicated conformational space of the five-membered sugar ring.[6] By convention, a phase angle $P = 0°$ corresponds to a perfect north conformation with a symmetrical twist form $^{3}_{2}$T, whereas its perfect south antipode $^{2}_{3}$T is

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Current address for Johannes H. Voigt, Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033.

Address correspondence to Victor E. Marquez, Laboratory of Medicinal Chemistry, NCI–Frederick, CCR, NCI, NIH, DHHS, 376 Boyles St., Frederick, MD 21702, USA; Fax: (301) 846-6033; E-mail: marquezv@mail.nih.gov

represented by $P = 180°$. The majority of nucleosides have P values in the vicinity of perfect north or south conformations.

A freely available Pseudo-Rotational Online Service and Interactive Tool (PROSIT) has been developed to rapidly access information about the state of the furanose moiety in nucleosides(tides).[7] Files containing 3D coordinates of any nucleoside(tide) can be submitted through a web browser at http://cactus.nci.nih.gov/prosit/. The tool automatically identifies all the nucleoside(tide) molecules in the file. The calculated P, ν_{max}, χ, and γ are tabulated in HTML format and displayed in the web browser.

After the first version of PROSIT was developed,[7] we realized that the criteria for defining a nucleoside(tide) was too strict and consequently some synthetic analogues were missed during the search. In an effort to expand the usefulness of PROSIT, we have since added a checkbox near the bottom of the file submission form. When this box is checked, PROSIT will report the pseudorotational parameters for any five-membered ring matching the pattern in Figure 1. Because this pattern does not test for the presence of a true nucleobase, the glycosyl torsion angle χ cannot easily be determined and is therefore arbitrarily set to 0.00°. Also, this choice is likely to include many non-nucleoside structures that the user will need to discard. However, this option ensures the recognition of most nucleoside(tide) analogues and therefore maximizes the usefulness of PROSIT. Such a feature has proved useful in the conformational analysis of an additional number of nucleoside analogues (Adelfinskaya, O., Bergstrom, D., private communication).

Using PROSIT, we have surveyed all the nucleosides found in the Cambridge Structural Database. Most of the more than 1100 β-D-nucleosides identified in high-resolution crystal structures have either a north-type configuration with P within 0–30°, or a south-type configuration with P within 150–180°.[7] The puckering amplitude ν_{max} values fall mainly in the range of 30–45°. The distributions obtained using PROSIT are very similar to previously reported figures.[8] Interestingly, a noticeable number of individual nucleosides appear to have unusual east, west, and even central ($\nu_{max} \approx 0°$) conformations. Results from quantum mechanical calculations indicate that these unusual conformations are directly caused by chemical modifications present in the sugar rings. These cases include an extremely high ν_{max} induced by a 2′-*O*,4′-*C*-methylene bridge in a north [2.2.1] bicyclic nucleoside and a rare east/central conformation induced by the C=C bond between carbons 2′ and 3′ in carbovir.[9]

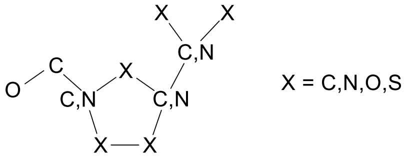


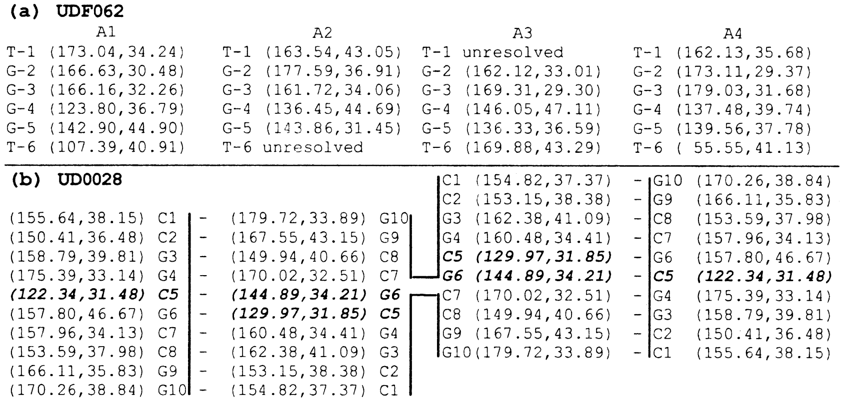
FIGURE 1 The relaxed substructure pattern used in PROSIT to search for additional nucleoside analogues.

A similar survey performed in the Nucleic Acid Database (NDB) found more than 1600 nucleotides in DNA or RNA strands in high-resolution structures. PROSIT analysis revealed that the nucleotides in DNA/RNA prefer the north or south conformations.[7] The east area is less populated than the north and south regions, while the central and west areas are virtually non-populated.

To demonstrate the usefulness of PROSIT, we show the results of two non-double-helical DNA structures with some interesting features. One DNA structure (NDB code: UDF062) consists of a stable parallel-stranded d(TG_4T) tetraplex of the kind formed by stretches of guanosines in the presence of Na^+ or K^+.[10] The calculated P and ν_{max} values for tetraplex (a) of the four-tetraplex asymmetric unit are listed in Figure 2a. In agreement with the literature results,[10] all except one of the 16 guanosines of the G_4 components of the tetraplex have south conformation with $136° < P < 180°$. One guanosine (G-4) in the A1 strand has a more eastern conformation with $P = 123.80°$.

The four-stranded Holliday junctions are critical intermediates in DNA recombination. Figure 2b shows the calculated P and ν_{max} values for the crystal structure of an antiparallel stacked-X form Holliday junction with the sequence d(CCGGCGCCGG) (NDB code: UD0028).[11] C5 of the outside non-crossover strand and C5G6 of the inside crossover strand have east sugar conformations, whereas the remaining nucleotides have south conformations. Since the crossover occurs between G6 and C7 of the inside strand, two nucleotides of the inside strand have east conformations before the crossover whilst those after the crossover have south conformations.

We hope that these examples have exemplified to the reader that the PROSIT web service, available at http://cactus.nci.nih.gov/prosit/, accurately reads a co-ordinate file and returns the phase angle P, puckering amplitude ν_{max} to produce a comprehensive report of the conformation of nucleosides(tides).



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(a)  UDF062
        A1                     A2                   A3                      A4
T-1 (173.04,34.24)     T-1 (163.54,43.05)  T-1 unresolved          T-1 (162.13,35.68)
G-2 (166.63,30.48)     G-2 (177.59,36.91)  G-2 (162.12,33.01)      G-2 (173.11,29.37)
G-3 (166.16,32.26)     G-3 (161.72,34.06)  G-3 (169.31,29.30)      G-3 (179.03,31.68)
G-4 (123.80,36.79)     G-4 (136.45,44.69)  G-4 (146.05,47.11)      G-4 (137.48,39.74)
G-5 (142.90,44.90)     G-5 (143.86,31.45)  G-5 (136.33,36.59)      G-5 (139.56,37.78)
T-6 (107.39,40.91)     T-6 unresolved      T-6 (169.88,43.29)      T-6 ( 55.55,41.13)
-------------------------------------------------------------------------------------
(b)  UD0028                                     |C1  (154.82,37.37)   - |G10 (170.26,38.84)
                                                |C2  (153.15,38.38)   - |G9  (166.11,35.83)
(155.64,38.15) C1  | -  (179.72,33.89) G10|     |G3  (162.38,41.09)   - |C8  (153.59,37.98)
(150.41,36.48) C2  | -  (167.55,43.15) G9 |     |G4  (160.48,34.41)   - |C7  (157.96,34.13)
(158.79,39.81) G3  | -  (149.94,40.66) C8 |     |C5  (129.97,31.85)   - |G6  (157.80,46.67)
(175.39,33.14) G4  | -  (170.02,32.51) C7 |_____|G6  (144.89,34.21)   - |C5  (122.34,31.48)
(122.34,31.48) C5  | -  (144.89,34.21) G6  _____ C7  (170.02,32.51)   - |G4  (175.39,33.14)
(157.80,46.67) G6  | -  (129.97,31.85) C5 |     |C8  (149.94,40.66)   - |G3  (158.79,39.81)
(157.96,34.13) C7  | -  (160.48,34.41) G4 |     |G9  (167.55,43.15)   - |C2  (150.41,36.48)
(153.59,37.98) C8  | -  (162.38,41.09) G3 |     |G10 (179.72,33.89)   - |C1  (155.64,38.15)
(166.11,35.83) G9  | -  (153.15,38.38) C2 |
(170.26,38.84) G10 | -  (154.82,37.37) C1 |
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FIGURE 2 The pseudorotational parameters (P and ν_{max} in degrees) of the nucleotides in (a) a parallel-stranded guanine tetraplex (UDF062) and (b) a stacked-X Holliday junction (UF0015).

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