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The *n*-propyl 3-azido-2,3-dideoxy-β-D-*arabino*-hexopyranoside: Syntheses, crystal structure, physical properties and stability constants of their complexes with Cu(II), Ni(II) and VO(II)

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ABSTRACT

The structure, conformation and configuration of the *n*-propyl 3-azido-2,3-dideoxy-β-D-*arabino*-hexopyranoside (**BAra-nPr**) were determined by ^{1}H NMR, ^{13}C NMR, and IR spectroscopy, as well as by optical rotation. The crystal structure was confirmed by single-crystal X-ray diffraction studies at room temperature. The compound crystallizes in $P2_1$ space group symmetry of the monoclinic system. The molecule has a $^4C_1$ chair conformation with azide group in the equatorial position both in a solution as well as in the crystal. The spatial arrangement of azide group is compared to other previously determined azidosugars. The hydrogen bonds between the hydroxyl group of sugar molecules lead to a ribbon structure observed also for the ethyl homolog. The packing of ribbons is dependent on the alkyl substituent length and with the elongation changes from pseudohexagonal to lamellar.

Acidity constants for the *n*-propyl 3-azido-2,3-dideoxy-β-D-*arabino*-hexopyranoside (**BAra-nPr**) in an aqueous solution were evaluated by the spectrophotometric and potentiometric titrations methods. Title compound exhibit blue absorption with the maximum wavelengths in the range of 266 nm and 306 nm. Based on these measurements we showed equilibria existing in a particular solution and a distribution of species which have formed during the titration.

We also investigated interactions between Cu(II), Ni(II) and VO(II) and title compound (as ligand L) during complexometric titration. On these bases we identified that in [Cu^{II}-**BAra-nPr**]$^{2+}$ the ratio of the ligand L to metal ion M(II) was 3:1, while in [Ni^{II}-**BAra-nPr**]$^{2+}$ and [VO^{II}-**BAra-nPr**]$^{2+}$ complexes 2:1 ratios were found. The cumulative stability constants (as log β) occurring in an aqueous solution for the complexes of **BAra-nPr** with Cu(II), Ni(II) and VO(IV) were 14.57; 11.71 and 4.20, respectively.

1. Introduction

In contrast to the chemistry of organic azides the chemistry of coordinated azides had received little attention until the early sixties. This was undoubtedly due to the explosive nature of metal azides and their extreme sensitivity to shock. However, when shock resistance and thermal stability became apparent for azido complexes that contain large counter ions or a central metal whose oxidation state is stabilized by certain ligands, this area of chemistry gained impetus. Indeed, a considerable amount of information concerning the chemistry of azido complexes is now available particularly owing to the efforts of W. Beck and his coworkers [1].

It is well known that the azide ion, N_3^-, is linear and symmetric, possessing equal N—N distances which average 1.154 Å. On the other hand the so-called covalent azides (HN_3 or organic azides) are linear and asymmetric with unequal N—N distances. In this case the longer bond distance always occurs between the middle nitrogen and the nitrogen which is bonded to the organic moiety. These distances together with the R—N_3 angle (the angle between the linear azide group and the R—N bonds) support Pauling's suggestion that the two canonical forms I and II are the main contributors to the ground-state geometry of the N_3 group (Fig. 1).

In contrast to the ionic or covalent azides the equilibrium configuration of coordinated azides is not as predictable. First of all the azide group can bound to one metal atom or act as a bridging

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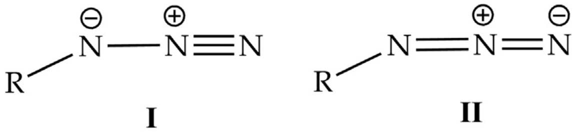

Fig. 1. Mesomeric structures of covalent organic azides.

group through one or two nitrogen atoms.

Our studies concern binding properties of azidosugar as a biologically important compound. Also, 3-azido-2,3-dideoxynucleosides seem to be promising agents against retroviral infections and especially human immunodeficiency virus (HIV) [2]. The interest of most researchers engaged in sugar chemistry has been focused on the search of simpler and more effective methods of synthesis of various sugar derivatives and their utilization as building blocks for further syntheses of bioactive compounds. Nonetheless, owing to the presence of electron donating functions carbohydrates and their derivatives constitute an impressive pool of potential bioligands involved in coordination of metal ions as well as in protonation and deprotonation reactions [3]. To examine one of this hypothesis we synthesized title compound and checked its ability to bind copper(II), nickel(II) and oxovanadium(II) ions. In our investigations presented in this work we also show its crystal structure and spectral properties.

2. Experimental

2.1. Materials and methods

All reagents for synthesis of the title compound as well as fixed solutions of hydrochloric acid and sodium hydroxide were purchased from Sigma-Aldrich Co.

The *n*-Propyl 3-azido-2,3-dideoxy-β-D-hexopyranoside (**BAra-nPr**) was synthesized using the method described in Ref. [4]. The optical rotation was determined at rt on a Perkin-Elmer polarimeter in a 1-dm tube at the D line of sodium using MeOH. Infrared spectra was recorded as Nujol mulls with a Bruker IFS 66 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 MHz instrument (400.49/100.70 MHz) in $CDCl_3$ with Me_4Si as the internal standard. Mass spectra was recorded with a Varian Matt 711 spectrometer with FD ionization mode. Elemental analysis was performed on a Carlo Erba EA 1108 analyzer. Melting point was uncorrected. Reactions were monitored by thin-layer chromatography (TLC) using aluminium-supported plates coated with E. Merck Kieselgel 60 F_{254} (0.02 mm, E. Merck, Darmstadt, Germany) with eluent systems (v:v) ethyl acetate – *n*-heptane of various ratio of solvents. To visualize the plate was burned in 200 °C. Column chromatography was performed on MN Kieselgel 60 (0.08 mm, E. Merck). Evaporations were carried out under diminished pressure at 35–40 °C on Büchi Rotavapor R-200.

2.2. Instrumental methods

Aqueous solutions of oxovanadium(IV) acetylacetonate, copper(II) chloride, nickel(II) chloride and monosaccharide (**BAra-nPr**) were prepared from purified water [5] before each measurement. The UV–Vis measurements were performed using *Perkin Elmer Lambda 45 UV/Vis* spectrophotometer at 20 °C. The temperature of analytes was maintained by the use of thermostat *Julabo* company coupled with the spectrophotometer and the quartz 4 ml cells (l = 1 cm). Titrant was added automatically by a titrator (*CerkoLab*®) coupled with the 1 ml *Hamilton* syringe terminated with Teflon needle (Gauge 20). The cells were provided with a magnetic stirrer and the system was connected to the PC computer with the *CerkoLab*® software. The range of measurement was 200–400 nm.

In the case of determination of the acidity constants by means of UV–Vis spectrophotometric titration [6] the analyte **BAra-nPr** was dissolved in a hydrochloric acid water solution (molar ratio **BAra-nPr**:HCl was 1:2). The titrant was a sodium hydroxide water solution. The same conditions were applied during the potentiometric titration method.

The complexometric titration procedure required a **BAra-nPr** water solution as an analyte, while the titrants were Cu(II) and Ni(II) salts containing saccharide at the same concentration as in the titrated solution [7]. In the last complex the analyte was VO(IV) in water while the titrant was saccharide containing oxovanadium(IV) acetylacetonate at the same concentration as in the titrated solution.

Absorption spectra of saccharide studied in an aqueous solution were compiled using *Origin 9.0 Software*. Water samples containing only monosaccharide were measured in a function of concentration at 20 °C. Absorbance *versus* concentration diagrams were linear in a measurable range, consistent with the Beer–Lambert law. The water solutions of **BAra-nPr** were colorless, therefore all the absorption spectra were made in the range 220–350 nm.

Values of an acidic constants distribution diagram of the relative concentration of variously protonated species as well as stability constants of complexes formed were estimated using EQUID program [8,9] based on the nonlinear least-squares Gauss–Newton–Marquardt algorithm [10].

2.3. X-ray measurements

Single crystals of **BAra-nPr** suitable for the X-ray diffraction experiment were recrystallized from a methanol solution. A selected, colourless crystal was measured at room temperature using mirror monochromated CuKα radiation on an Oxford Diffraction κ-CCD Gemini An Ultra diffractometer. Cell refinement and data collection as well as data reduction and analysis were performed with the CRYSALIS^{PRO} software [11]. The structure was solved by direct methods using the SHELXT [12] structure solution program and refined by full matrix least squares against F^2 with the SHELXL [13] implemented in the OLEX2 [14] suite. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms attached to carbon atoms were added to the structure model at geometrically idealized coordinates and refined as riding atoms with $U_{iso}(H) = 1.2 \times U_{eq}(CH \text{ and } CH_2)$ or $U_{iso}(H) = 1.5 \times U_{eq}(CH_3)$. The position of hydrogen atoms of the hydroxyl groups was refined freely but with a restraint O–H distance to 0.82(1)Å. An absolute configuration for the molecule was established basing on reaction and anomalous dispersion effects. A total of 949 Bijvoet pairs with coverage of 0.98 were included in the further calculations. The resulting value of the Hooft parameter [15] was 0.09(18) with a *P*2 probability for an inverted structure smaller than 1×10^{-6} what indicates correct absolute structure assignment. Flack parameter [16], *x*, calculated from 697 selected quotients (Parsons' method) [17] equals −0.053(207). Additionally, an inversion of the structure leads to an increase of the *R*1 parameter from 4.10% to 4.11%.

2.4. Physicochemical and spectral data

Mp 73–75 °C, $[\alpha]_D$ −6 (c 0.8, MeOH), R_f 0.3 (1:2 *n*-heptane–ethyl acetate); IR [cm^{-1}]: 3278 (m broad, intermolecular H bonds –OH), 2984 and 2925 (m sharp; C–H), 2844 (m sharp; $-O-CH_2-$), 2097 (assym. sharp; –N=N– in $-N_3$), 1356 (*sym.* sharp; –N=N– in $-N_3$), 688 (bent R–N–N–N in $-N_3$), 619 (torsion; –N–N–N in $-N_3$), 1081 (m sharp; C–O in $-CH_2-OH$), 1045 (m sharp; C–O–C);

^{1}H NMR, *δ* [ppm]: 4.57 (dd, 1H, $J_{1,2a}$ 9.6 Hz, $J_{1,2e}$ 2 Hz, H-1), 3.84