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Tris(pyrazolyl)methanesulfonates: A Novel Class of Water-Soluble Ligands

Wolfgang Kläui,* Michael Berghahn, Gerd Rheinwald, and Heinrich Lang

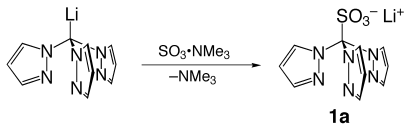
In 1966 Trofimenko introduced a new tripodal nitrogen-donating ligand, hydrotris(pyrazolyl)borate, into coordination chemistry. Soon these anions found their way into coordination chemistry as versatile nitrogen-based chelating ligands. Nowadays the substituted hydrotris(pyrazolyl)borates (in the following abbreviated as Tp) are the most important class of N_3 tripodal ligands.[1] The possibility of increasing the steric demands of the ligand through bulky substituents in the 3-position of the pyrazole ring is an important aspect in the chemistry of Tp ligands.[2] Such sterically demanding Tp ligands play an important role in the synthesis of various enzyme models.[3]

Vahrenkamp and co-workers were able to obtain a Zn–hydroxide complex with $Tp^{Cum,Me}$ ligands[4] which showed, for example, hydrolytic activity towards activated esters, amides, and nonactivated phosphate esters, and thus functioned as a stoichiometric model for esterases, peptidases, and phosphatases.[5] However, due to the insolubility of this particular complex in water it is neither possible to determine a pK_s value for a zinc-bound water molecule in aqueous solution, nor is it possible to add water during the hydrolysis reaction to regenerate the $Tp^{Cum,Me}$-Zn-OH complex. Therefore, the hydrolysis reaction shows only stoichiometric not catalytic behavior.[6] Another problem is the sensitivity of the B–N bond in hydrotris(pyrazolyl)borate ligands to hydrolysis. Even by substituting the proton in the 5-position of the pyrazolyl ring with a methyl group, the hydrolysis of the B–N bond cannot be completely avoided.[7]

Especially in the field of enzyme models it is of great interest to obtain complexes that are soluble and stable under physiological conditions. The introduction of functional groups that would generate water solubility in hydrotris(pyrazolyl)borate is still an unsolved problem to date. With this in mind, our aim was to find a ligand that would prove to be water-soluble and stable towards hydrolysis, and thus could be used as an alternative to hydrotris(pyrazolyl)borates.

A suitable ligand system should have a similar arrangement of the donor centers as in hydrotris(pyrazolyl)borate and offer the possibility to introduce hydrophilic groups in a straightforward manner. We have found that the isosteric and isoelectronic tris(pyrazolyl)methane ligand proved to be a suitable starting material. In this class of ligands, first published by Hückel and later made more easily accessible by a more facile preparation reported by Juliá, the B–N bonds are substituted by C–N bonds.[8, 9] The methine proton of tris(pyrazolyl)methane is sufficiently acidic to be removed by butyllithium, and the resulting reactive intermediate readily reacts with electrophiles.[10]

Since our goal was the introduction of a hydrophilic moiety, we added the lithiated tris(pyrazolyl)methane to a sulfurtrioxide–trimethylamine complex and obtained the lithium salt of tris(pyrazolyl)methanesulfonic acid (**1a**; LiTpms) as shown in Equation (1). A metathesis reaction of **1a** with potassium carbonate gave the corresponding potassium salt (**1b**; KTpms).



1a (1)

In contrast to tris(pyrazolyl)methane, **1b** is almost exclusively soluble in water and only moderately soluble in methanol. Another distinct difference to tris(pyrazolyl)methane[11] and especially to hydrotris(pyrazolyl)borate is the fact that the reported ligand Tpms (**1**) is stable over a wide range of pH values in aqueous solution. At pH 0 only small amounts of pyrazole—the product resulting from a hydrolysis

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reaction—can be detected even after several weeks, at pH 13 even after weeks no signs of decomposition can be detected.

Regarding the use of tris(pyrazolyl)methanesulfonate as a novel class of ligands as enzyme models, we prepared the sterically demanding ligand tris(3-*tert*-butylpyrazolyl)methanesulfonate **2a** (LiTpms$^{t\mathrm{Bu}}$[12]), starting from tris(3-*tert*-butylpyrazolyl)methane in a reaction analogous to the synthesis of **1**. The corresponding thallium salt **2b** (TlTpms$^{t\mathrm{Bu}}$) can be obtained by a metathesis reaction with thallium nitrate in a mixture of methanol and water. Owing to the facile removal of thallium salts, **2b** is an excellent starting material for complexation reactions. The molecular structure of **2b** was solved by X-ray diffraction (Figure 1).[13] TlTpms$^{t\mathrm{Bu}}$ is stable towards protic solvents and decomposes only in the presence of mineral acids with formation of pyrazole.

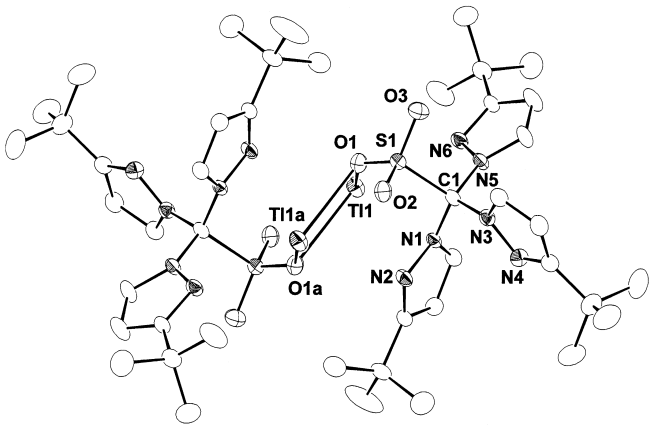

Figure 1. Crystal structure of **2b**. Selected distances [Å] and angles [°]: Tl1-O1 2.708(3), Tl1-Tl1a 4.1537(3), S1-O3 1.434(3), S1-O2 1.456(3), S1-O1 1.465(3), S1-C1 1.891(4), O1-Tl1a 2.748(3), N1-N2 1.371(4), N1-C1 1.448(5), N3-N4 1.374(5), N3-C1 1.451(5), N5-N6 1.374(5), N5-C1 1.452(5); O1-Tl1-O1a 80.86(10), O1-Tl1-Tl1a 40.79(6), O1a-Tl1-Tl1a 40.07(6), O2-S1-O1 111.72(18), O1-S1-C1 102.71(17), S1-O1-Tl1 100.26(15), S1-O1-Tl1a 135.99(17), Tl1-O1-Tl1a 99.14(10), N1-C1-N3 109.6(3), N1-C1-N5 109.5(3), N3-C1-N5 108.6(3), N1-C1-S1 110.5(2), N3-C1-S1 110.4(3), N5-C1-S1 108.2(3).

Preliminary experiments demonstrate that the ligand Tpms$^{t\mathrm{Bu}}$ (**2**) forms tetrahedral complexes with transition metals that are C_{3v}-symmetric according to spectroscopic evidence.[14] The ligand **1** forms sparingly soluble precipitates with divalent metal ions of the general composition M(Tpms)$_2$. In this respect **1** shows similar behavior as the unsubstituted Tp ligand. The solubility of Tpms in protic solvents allows, for example, the synthesis of [(Tpms)Cu(CO)], a methanol-soluble copper(I) carbonyl complex which proves to be thermally stable but sensitive towards oxidation. Evidently, Tpms (**1**) and Tpms$^{t\mathrm{Bu}}$ (**2**) serve as tripodal nitrogen-donating ligands.

Preliminary experiments have shown that it is possible to introduce hydrophilic substituents other than sulfonate. For example, the reaction of lithium tris(pyrazolyl)methanide with carbon dioxide or ethylene oxide gave the corresponding water-soluble carboxylic acid or alcohol. Numerous ways of further derivatization are possible, which should lead to stable ligands, hopefully with an even higher water-solubility, that can be used in enzyme models.

Experimental Section

1a, **b**: *n*-Butyllithium (4.7 mL of a 1.6 M solution) was added to a solution of tris(pyrazolyl)methane (1.3 g, 6.1 mmol) in THF (25 mL) at −60 °C. The solution immediately turned yellow and turbid. After one hour sulfurtrioxide-trimethylamine complex (1.0 g, 7.5 mmol) was added at −50 °C. Under constant stirring, the resulting suspension was allowed to warm to 0 °C over 90 min. After another three hours the solvent was evaporated. To remove excess tris(pyrazolyl)methane, the residue was treated with chloroform, stirred for one hour, and eventually filtered over a membrane filter. Recrystallization from hot methanol yielded colorless crystals of LiTpms (**1a**) (0.88 g, 48 %). Elemental analysis (%) calcd for $C_{10}H_9LiN_6O_3S$: C 40.0, H 3.0, N 28.0; found: C 40.0, H 3.1, N 28.2.

Alternatively, KTpms was isolated from the crude product by a metathesis reaction with potassium carbonate in a mixture of water and methanol. Evaporation of the solvent mixture and subsequent recrystallization from hot methanol gave colorless crystals of KTpms (**1b**) (0.72 g, 37 %). ^{1}H NMR (200 MHz, D_2O, 300 K): $\delta = 6.5$ (dd, $^3J(H,H) = 2.8$, 1.8 Hz, 1H; 4-H), 7.6 (dd, $^3J(H,H) = 2.8$, $^4J(H,H) = 0.6$ Hz, 1H; 3- or 5-H), 7.7 (dd, $^3J(H,H) = 1.8$ Hz, $^4J(H,H) = 0.6$ Hz, 1H; 3- or 5-H); ^{13}C{^{1}H} NMR (500 MHz, D_2O, 300 K): $\delta = 96.4$, 108.4, 132.9, 142.7; elemental analysis (%) calcd for $C_{10}H_9KN_6O_3S$: C 36.1, H 2.7, N 25.3; found: C 36.1, H 2.3, N 25.0.

2a, **b**: LiTpms$^{t\mathrm{Bu}}$ was prepared in analogy to the synthesis of LiTpms from tris(3-*tert*-butylpyrazoyl)methane.[15] The thallium salt was obtained by reaction of LiTpms$^{t\mathrm{Bu}}$ (0.23 g, 0.48 mmol) with $TlNO_3$ (0.25 g, 0.95 mmol) in a methanol/water mixture (1/1; 30 mL). Compound **2b** precipitated as an analytically pure white powder (0.25 g, 75 %). Crystallization from methanol yielded colorless crystals suitable for X-ray structure analysis. ^{1}H NMR (200 MHz, $CDCl_3$, 300 K): $\delta = 7.5$ (d, $^3J(H,H) = 2.7$ Hz, 1H, 5-H), 6.3 (d, $^3J(H,H) = 2.7$ Hz, 1H, 4-H), 1.3 (s, 9H, CH_3); ^{13}C{^{1}H} NMR (500 MHz, $CDCl_3$, 300 K): $\delta = 31.1$, 32.9, 96.8, 105.0, 134.0, 165.0; elemental analysis (%) calcd for $C_{22}H_{33}N_6O_3STl$: C 39.7, H 5.0, N 12.6; found: C 39.7, H 4.9, N 12.7.

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[12] The abbreviation is used in analogy to the nomenclature of Trofimenko.[1b]

[13] Crystal structure analysis of **2b**: crystal dimensions $0.45 \times 0.35 \times 0.25$ mm^3, triclinic, $P\bar{1}$, $a = 10.5675(1)$, $b = 10.7703(1)$, $c = 11.7191(2)$ Å, $\alpha = 87.3920(8)$, $\beta = 74.4663(1)$, $\gamma = 81.2366(7)°$, $V = 1270.07(3)$ Å^3, $Z = 1$, ρcalcd $= 1.741$ g cm^{-3}, $F(000) = 656$, $T = 173(2)$ K, The measurement was performed on a Bruker axs-

diffractometer with a smart CCD detector ($Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, ω scans, $3.6 \leq 2\theta \leq 60.74^\circ$). All in all 10263 reflections were detected (6663 independent reflections) and 5869 were classified as observed. The structure was solved by direct methods and refined against F^2. Hydrogen atoms were placed at calculated positions and refined dependent on the adjacent non-hydrogen atoms (riding model). The refinement of the 331 varied parameters converged to $R = 0.0425$ for 6663 reflections with $I > 2\sigma(I)$ and $wR2 = 0.0900$ for all reflections. Min./max. transmission 3.790/2.057 e Å^{-3}. The structure was solved with SIR-97[16] and refined with SHELXL-97.[17] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-141108. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[14] In poorly solvating solvents the reaction of TlTpms^{rBu} with $ZnBr_2$ leads to not only the expected C_{3v}-symmetrical species but also to a C_s-symmetrical compound that has yet to be identified.

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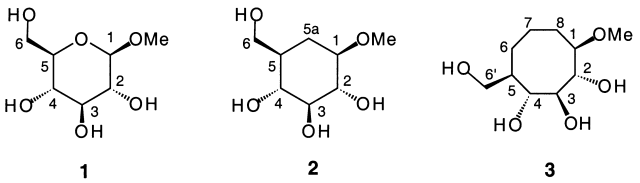
From Glucose to Cyclooctanic Carbaglucose: A New Class of Carbohydrate Mimetics

Wei Wang, Yongmin Zhang, Matthieu Sollogoub, and Pierre Sinaÿ*

Synthetic oligosaccharides have recently emerged as potential therapeutic agents.[1] A possible in vivo hydrolysis of such drugs by various glycosidases has stimulated the search for nonhydrolyzable oligosaccharide mimetics. One option is to replace the endocyclic oxygen atom of aldohexopyranosyl residues by a methylene group. The resulting 5a-carbasugars are hydrolytically stable analogues, and the chemical synthesis of the 5a-carbaaldohexopyranoside family has been largely developed.[2] An intriguing alternative is to use a cyclooctane ring as a framework for the OH groups of the carbohydrate. For instance, the replacement of the endocyclic oxygen atom in methyl β-D-glucopyranoside (**1**) by one methylene group would result in a cyclohexanic mimetic **2**, whereas the replacement by three methylene groups would give a novel type of cyclooctanic carbohydrate mimetic **3** (Scheme 1).

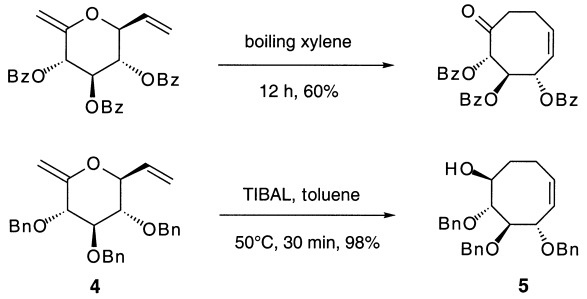
The rationale behind this proposal is that the conformation and conformational equilibration of cyclooctane derivatives[3] may offer interesting new distributions of hydroxy groups



Scheme 1. Methyl β-D-glucopyranoside (**1**) as well as the cyclohexanic (**2**) and cyclooctanic (**3**) analogues.

compared to those available through the classical pseudorotational itinerary[4] of pyranoid rings. The incorporation of these so far undescribed carbocyclic sugar mimetics in oligosaccharide chains is thus of interest in terms of the resulting biological responses, such as glycosidase inhibition, a feature which may benefit from the easy access to nonclassical conformers.

The thermal or triisobutylaluminum (TIBAL) promoted Claisen rearrangement of 2-methylene-6-vinyl-tetrahydropyran, which affords cyclooctanic derivatives by insertion of a C_2 unit, has been elegantly developed by Paquette et al.[5] for the synthesis of natural products with eight-membered rings. It has recently been applied in the carbohydrate field, either in the form of a thermal reaction,[6] or in the form of a smooth Al^{III}-catalyzed process[7] (Scheme 2).



Scheme 2. Thermal or TIBAL-catalyzed Claisen rearrangement of unsaturated monosaccharide derivatives. Bn = $PhCH_2$; Bz = PhCO.

As shown in Scheme 3, the cyclooctanol derivative **6**, the enantiomer of the previously prepared cyclooctanol **5**, was smoothly obtained in 96% yield from the TIBAL-catalyzed sigmatropic rearrangement of the gluco derivative **12**, which in turn was easily derived from methyl α-D-glucopyranoside in an eight-step sequence.

Methylation of **6** gave **13** which, upon regio- and stereoselective hydroboration, was converted in 60% yield into the cyclooctanol derivative **14** (Scheme 4). Oxidation of **14** gave the cyclooctanone **15**, and subsequent treatment with the Tebbe reagent $[Cp_2Ti(\mu\text{-}Cl)(\mu\text{-}CH_2)AlMe_2]$ generated the methylene derivative **16**. Regioselective hydroboration of **16** gave the cyclooctanic mimetic **17** and the α-L-ido isomer **18**, which were separated by flash chromatography on silica gel (Scheme 5).

The boat–chair conformation for compound **17** (Scheme 6) is assigned on the basis of the ^3J couplings in the ^{1}H NMR spectrum. The H1–H5 NOE confirms the β-D-gluco configuration. The interpretation of the NMR spectrum of the α-L-

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