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Hinge Sugar as a Movable Component of an Excimer Fluorescence Sensor

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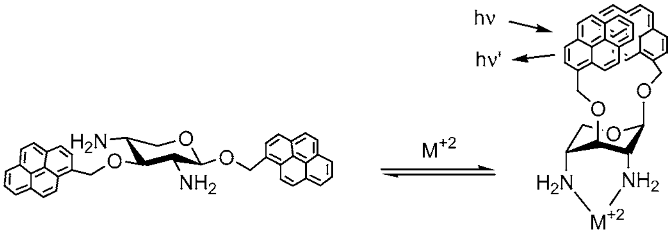
ABSTRACT



The ring flip of a carbohydrate is employed for the tongs-like movable component of a metal ion sensor. A pair of separated pyrene groups attached to the carbohydrate component are placed side by side when it recognizes metal ions, affording excimer fluorescence. This novel molecular sensor is selective for Zn^{2+} and Cd^{2+}.

The functions of a number of supramolecules, molecular devices, and molecular machines rely on their conformational changes.[1] Some of these conformational changes are based on the ring flip of cyclohexane, which has been employed[2] for the movable component of pyrene-based excimer fluorescence sensors.[3] These sensors have the recognition and reporter components, respectively, on each side of the cyclohexane plane, mimicking the fundamental design of signal transducers at the interface across a cell membrane. When these sensors catch ligands on the recognition side by rearranging their diequatorial arms into diaxial orientation, the stacked pyrene groups attached to the diaxial arms on the reporter side are forced to unstack with the arms rearranged into diequatorial orientation in a clothespin manner, which in turn extinguishes the excimer fluorescence. This clothespin-like motion is considered easier to accomplish with cyclohexane than a tongs-like motion that requires highly constrained four axial arms in its closed form. In this paper, we present a tongs-like excimer fluorescence sensor based on the ring flip of a xylopyranoside,[4] which generates eximer fluorescence when ligand is bound, that is, a response opposite to the clothespin-like sensors. In the closed form of the tongs-like sensor, the pivot xylopyranoside assumes a $^1C_4$ conformation with four axial substituents. This sterically demanding structure is facilitated by the peculiar properties of carbohydrates, i.e., the anomeric effect and the absence of hydrogen atoms on the ring oxygen.[5]

Methyl 2,4-disubstituted β-D-xylopyranosides are known to favor $^1C_4$ over $^4C_1$ conformations[6] in nonpolar solvents, presumably due to the intramolecular hydrogen bond between

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[1] (a) Balzani, V.; Venturi, M.; Credi, A. *Molecular Devices and Machines*; VCH: Weinheim, 2003. (b) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **2000**, *39*, 3348−3391. (c) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; John Wiley & Sons: Chichester, 2000.

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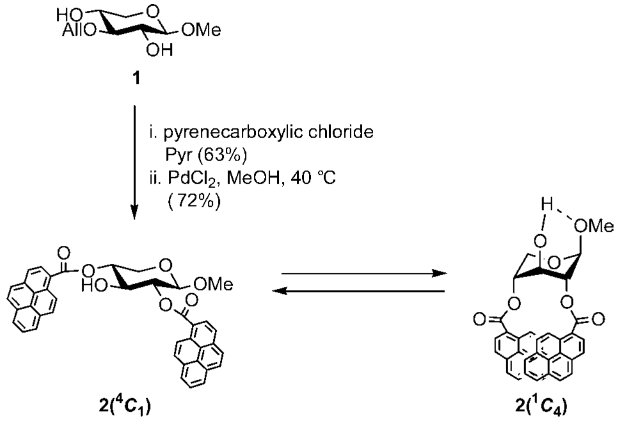
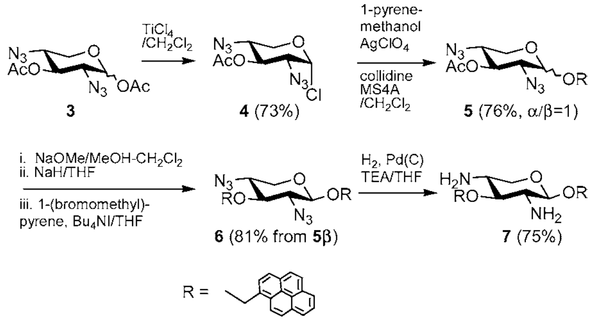
Scheme 1



3-OH and 1-O.[7] Thus, we first examined whether the 2,4-di-*O*-pyrenecarbonyl-substituted derivative **2** also prefers $^1C_4$ conformation and forms an excimer complex in nonpolar solvents and yet assumes $^4C_1$ conformation in polar solvents such as DMSO by interfering with the hydrogen bonding. This facile conformation change of pyranoside even with the large substituents is prerequisite for sensitive molecular sensors. Compound **2** was prepared by pyrenecarbonylation of methyl 3-*O*-allyl-*β*-D-xylopyranoside **1**[8] and subsequent deallylation (Scheme 1). From the *J*-values,[9] compound **2** existed in equilibrium between $^4C_1$ and $^1C_4$ conformations in each solvent and the percentages of $^1C_4$ conformation of **2** were estimated[10] to be 93% in $CDCl_3$, 64% in CD_3OD, and 22% in DMSO-d_6. These data demonstrate that the gained stability of the $^1C_4$ structure in $CDCl_3$ compared with that in DMSO-d_6 is approximately 2.3 kcal/mol, being in the range of a single OH...O hydrogen bond.[11] Moreover, IR spectra of **2** in CCl_4 indicates an absorption band at 3530 cm^{-1}, which is attributed to the intramolecular hydrogen bond that constructs the six-membered ring, as depicted in structure **2(^{1}C$_4$)**.[7] In line with the above results, the excimer fluorescence at about 500 nm was observed with **2** in the less polar solvent, $CHCl_3$, probably because the two pyrene groups were placed in close proximity with the $^1C_4$ conformation. Moreover, the polar solvents, e.g., MeOH and DMSO, tend to decrease the excimer fluorescence, probably because the hydrogen-bonding is interrupted in these solvents (Figure 1A).[12] Thus, the hydrogen bonding is the most plausible driving force for the closing-tongs-like motion of compound **2**, giving the excimer complex. The lower limit of the concentration of **2** to observe the excimer fluorescence was 10 nM in $CHCl_3$.

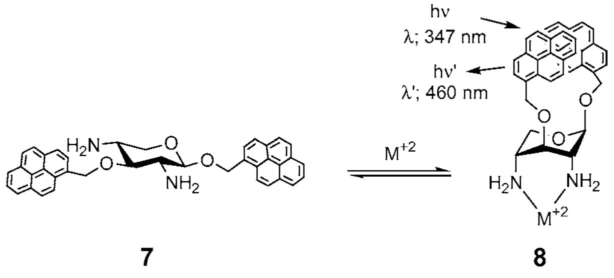
Scheme 2



Since as small a force as a single hydrogen bonding is enough to switch the excimer fluorescence with compound **2**, the xylopyranose-based excimer fluorosensors will find a number of applications. We designed 2,4-diaminoxylopyranoside **7** as a common reporter component for various molecular sensors. The amino group of **7** can be a universal connector for various recognition components, and the amino group as itself can be a recognition site for metal ions. Compound **7** was synthesized from 2,4-diazido-xylopyranose **3**[4a] (Scheme 2). Compound **3** was converted to glycosyl chloride **4** with $TiCl_4$, which was then subjected to a typical glycosidation conditions for 2-azido-2-deoxy-glycosyl chlorides to give pyrenylmethyl xyloside **5**. Deacetylation and O-alkylation at the 3-position of compound **5** gave compound **6**, which was subjected to the reduction of the azido groups to give the desired compound **7**.

NMR measurements revealed that compound **7** assumed $^4C_1$ conformation in all solvents tested ($CDCl_3$, acetone-d_6, DMF-d_7, and DMSO-d_6).[13] However, the addition of $ZnCl_2$ (5 equiv) to the acetone-d_6 solution immediately changed the conformation of **7** into $^1C_4$ as indicated by their small ^3J-values[14] (Scheme 3, Figure 2). The predominant formation of $^1C_4$ was unexpected, because our previous studies[4a] demonstrated that the addition of Zn^{2+} to the aqueous

Scheme 3



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(9) **2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02−7.34 (m, 18H, Ar), 5.33−5.30 (m, 2H, H-2, H-4), 5.11 (d, 1H, $J_{1,2} = 2.1$ Hz, H-1), 4.58 (dt, 1H, $J_{2,3} = J_{3,4} = 4.0$ Hz, $J_{3,OH} = 8.9$ Hz, H-3), 4.52 (dd, 1H, $J_{4,5a} = 2.6$ Hz, $J_{5a,5b} = 13.3$ Hz, H-5a), 4.07 (dd, 1H, $J_{4,5b} = 2.3$ Hz, H-5b), 3.63 (s, 3H, OMe), 3.57 (d, 1H, OH).

(10) Optimized structures of **2** with $^4C_1$, $^1C_4$, $^2S_0$, $^3S_1$, and ^{03}B conformations were calculated by PC Spartan Plus software (Wavefunction, Inc.) using SYBYL force field. The calculated *J*-values were derived from the calculated dihedral angles by the generalized Karplus equation (Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783−2792.). The least-squares fitting of the calculated *J*-values to the observed values was performed by multiple-regression analysis using Sigma Plot 2000 software (SPSS, Inc.) to give the $^1C_4$ abundance. The populations of the skew and boat conformations were negligible.

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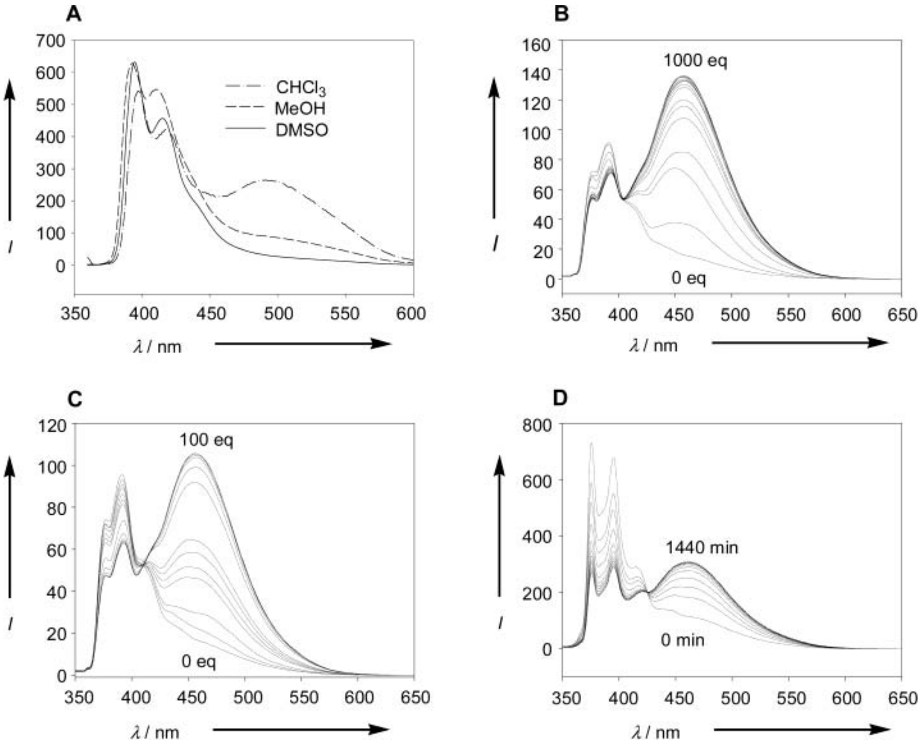

Figure 1. (A) Solvent-dependent excimer fluorescence of **2** (1 μM) with the excitation at 355 nm. Intensity scales are 5-fold for $CHCl_3$ solution and 2-fold for MeOH solution. (B) Fluorescence spectral change of **7** (1 μM in acetone; exitation at 347 nm) with the addition of $ZnCl_2$ (0, 0.5, 1, 2, 3, 4, 5, 10, 20, 30, 40, 50, 100, 300, 500, 1000 equiv). (C) Fluorescence spectral change of **7** (1 μM in acetone; exitation at 347 nm) with the addition of $CdCl_2{\cdot}4H_2O$ (0, 0.5, 1, 2, 3, 4, 5, 10, 20, 30, 40, 50, 100 equiv). (D) Time course for the fluorescence spectral change of **7** (1 μM in DMSO; exitation at 347 nm) after the addition of $K_2[PtCl_4]$ (1 equiv). The reaction was monitored at 0, 30, 60, 120, 240, 360, 480, 600, 720, 960, 1200 and 1440 min.

solution of a simple hinge sugar derivative resulted in a $^4C_1$−$^1C_4$ equilibrium with a $^1C_4$ proportion of at most 40%. Perhaps the stacking force between two pyrene groups assisted the predominant $^1C_4$ formation. The $^4C_1$ structure was recovered by the addition of 4 equiv of triethylenetetramine to **7**−Zn^{2+} complex. The addition of $K_2[PtCl_4]$ to the DMF-d_7 solution of **7** converted it to $^1C_4$ conformation after 15 h, as expected from our similar studies[4b] with a hinge sugar derivative. The complex **8(M=Pt)** with $^1C_4$ conformation was isolable.[15]

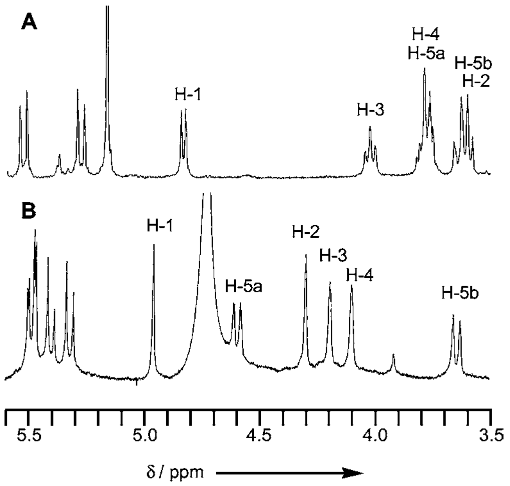

Figure 2. (A) ^{1}H NMR spectrum of **7** in acetone-d_6. (B) ^{1}H NMR spectrum of **7** with 5 equiv of $ZnCl_2$ in acetone-d_6. Assignments were based on COSY, HMQC, and HMBC.

As with 2,4-dipyrenyl compound **2**, $^1C_4$ conformation forces the two pyrenyl groups of **8** into 1,3-diaxial orientation, which would facilitate formation of the excimer complex. In practice, addition of $ZnCl_2$ to the acetone solution of **7** caused the eximer fluorescence at around 480 nm (Figure 1B), as expected from the formation of $^1C_4$ conformation in the NMR experiments. The minimum concentration of Zn^{2+} required to observe the excimer

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(12) With methyl 2,4-diamino-2,4-dideoxy-2,4-di-*N*-pyrenecarbonyl-β-D-xylopyranoside, excimer fluorescence was not observed in any solvents tested for compound **2**.

(13) NMR measurements were restricted by the limited combination of compound **7** and metal ions in solubility to the solvents and by paramagnetic properties of metal ions.

(14) **8(M=Zn)**: ^{1}H NMR (400 MHz, acetone-d_6) δ 8.28−7.60 (m, 18H, ArH), 5.49 (d, 1H, J = 11.3 Hz, CH_2Ar), 5.48 (d, 1H, J = 11.9 Hz, CH_2-Ar), 5.40 (d, 1H, J = 11.6 Hz, CH_2Ar), 5.32 (d, 1H, J = 11.9 Hz, CH_2Ar), 4.96 (s, 1H, H-1), 4.60 (dd, 1H, $J_{4,5a}$ = 2.3, $J_{5a,5b}$ = 12.2 Hz, H-5a), 4.30 (s, 1H, H-2), 4.19 (s, 1H, H-3), 4.10 (s, 1H, H-4), 3.65 (d, 1H, H-5b).

(15) **8(M=Pt)**: ^{1}H NMR (400 MHz, DMF-d_7,) δ 8.51−7.72 (m, 18H, Ar), 5.55, 5.39, 5.33, 5.27 (d × 4, 1H × 4, J = 11.7, 12.2, CH_2Ar), 5.36 (s, 1H, H-1), 4.44 (d, 1H, $J_{5a,\,5b}$ = 12.5 Hz, H-5a), 3.96 (s, 1H, H-2), 3.90 (d, 1H, H-5b), 3.20(s, 1H, H-3), 2.92 (m, 1H H-4).

fluorescence was 50 nM with 100 nM of [**7**], comparable to most metal ion sensors.[16] $CdCl_2$ also caused the excimer fluorescence as shown in Figure 1C. Interestingly, the other metal ions (Li^+, Na^+, Cr^{3+}, Fe^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zr^{2+}, Ag^+, Ba^{2+}, La^{3+}, Pb^{2+}) did not exhibit significant excimer fluorescence, while $HgCl_2$, $MnCl_2$, and $Mg(ClO_4)_2$ showed slight excimer fluorescence. Thus, the sensor **7** is selective for Zn^{2+} and Cd^{2+} as with the other fluorescence sensors.[16a,17] These sensors show a fluorescence enhancement only when the nonquenching diamagnetic ions, Zn^{2+} and Cd^{2+}, are bound. On the other hand, Zn^{2+} caused no excimer fluorescence in DMSO. Furthermore, a small amount of DMSO (0.1% v/v) was sufficient to completely extinguish the excimer fluorescence of the acetone solution. Perhaps, the oxygen atom of sulfoxide is more nucleophilic than that of acetone, interfering with the chelation.[18] The better H-bond-accepting ability of DMSO[19] relative to acetone could also play a roll. However, addition of $K_2[PtCl_4]$ to the solution of **7** in DMSO induced the excimer fluorescence at around 480 nm, which increased over 18 h to reach a plateau (Figure 1D). Unfortunately, **7** was insoluble in water, limiting the convenience of this sensor.

In conclusion, we demonstrate here the application of the hinge sugar in an excimer fluorescence sensor selective for Zn^{2+} and Cd^{2+}. To the best of our knowledge, this is the first report of a carbohydrate-based movable device. Since the amino functional group used for the recognition of metal ions can be modified with a variety of ligands recognized by metal ions, receptor proteins, and DNA, compound **7** will be the basic sensor component.

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Supporting Information Available: Synthetic details and characterization for all new compounds and general experimental procedures and fluorescence and NMR spectra for compound **7** with metal ions. This material is available free of charge via the Internet at http://pubs.acs.org.

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