Inorg. Chem. **2006**, *45*, 5315–5320

Inorganic Chemistry
Article

Sensitive and Selective PET-Based Diimidazole Luminophore for Zn^{II} Ions: A Structure–Activity Correlation

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Received November 2, 2005

3-(3-Ethoxymethyl-1H-imidazol-2-yl)-3-(1-ethoxymethyl-1H-imidazol-2-yl)-3H-benzo[de]isochromen-1-one, **4**, is a novel photoinduced electron transfer (PET) chemosensor that becomess fluorescent upon binding metal ions and shows a strong preference toward Zn^{II} ions. The new bisimidazol PET sensor and its zinc complex were prepared and characterized in terms of their crystal structures, absorption and emission spectra, and orbital energy diagrams. Free **4** is a weakly luminescent species. On the basis of detailed DFT calculations, we suggest that the poor luminescence yield of free **4** originates from its orbital structure in which two π-orbitals of the two imidazole rings, HOMO and HOMO–1, are situated between two π-orbitals of the isochromene-one system, HOMO–2 and LUMO. The absorption and emission processes occur between the two π-orbitals of the isochromene-one system, HOMO–2 and LUMO, and the two π-imidazole orbitals serve as quenchers for the excited state of the molecule through nonradiative processes. Upon binding Zn^{II} ions, **4** becomes a highly luminescent species having a luminescence maximum peaking at 375 nm ($\lambda_{ex} = 329$ nm). The significant 900-fold enhancement in luminescence upon binding of the Zn^{II} ions is attributed to the stabilization of the π-orbitals of the imidazole rings upon their engagement in new bonds with the zinc ion. The affinity of **4** to zinc ions in acetonitrile is found to be very high, $K_a > 3 \times 10^6\ M^{-1}$, while with other metals ions, the association constants are considerably weaker.

I. Introduction

The development of fluorescent indicators that are sensitive to biologically relevant substrates such as zinc,[1] magnesium,[2] and alkali metal cations,[3] as well as to different anions such as halides[4] and carboxylates,[5] is of enormous interest to biology-related research, as well as to the field of medical diagnostics.

Of all possible detection mechanisms, photoinduced energy transfer (PET) appears to be the most elegant, sensitive, and effective way to report the presence of substrates such as protons,[6] metal ions,[7,1f] anions,[8,4a−c] and even uncharged molecules.[9]

First proposed by Weller[10] and perfected by De Silva[11,1f] and others,[12] the PET chemosensor consists of a luminescent species attached to a recognition group, Scheme 1.

In the unbound dark state of these systems, the binding group efficiently quenches the excited state of the luminescent part. This is normally achieved through electron/energy transfer processes that take place between the lone pair

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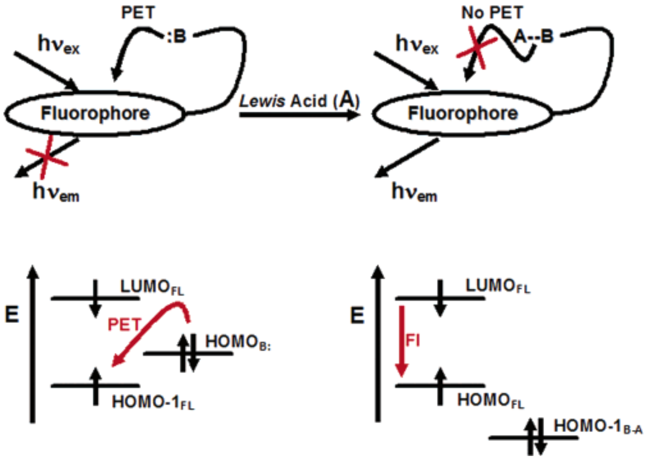
Scheme 1. Mechanism and a Generalized Energy Diagram of PET-Based Sensing



electrons of the recognition groups and the relevant orbitals of the luminophore that are involved in the optical absorption and emission processes. The same lone pair electrons also bind the metal ions and protons to the recognition group. Therefore, upon binding, the lone pair of the recognition group becomes engaged in the newly formed bond and can no longer serve as an efficient quencher for the luminophore. Thus, these kinds of systems regain their luminescence upon binding a guest and are therefore capable of signaling its capture.

Here, we report on the preparation of a new bisimidazole-based PET receptor for zinc ions. 3-(3-Ethoxymethyl-1H-imidazol-2-yl)-3-(1-ethoxymethyl-1H-imidazol-2-yl)-3H-benzo[de]isochromen-1-one is a novel PET chemosensor which becomes fluorescent when it binds $\mathrm{Zn}^{\mathrm{II}}$ ions. The new bisimidazole and zinc complexes were prepared and characterized in terms of their crystal structures, absorption and emission spectra, and orbital energy diagrams.

II. Experimental Section

II.a. Apparatus. NMR spectra were recorded on a Brucker AC-200F spectrometer. Mass Spectra were recorded using a triple quadrupole TSQ-70 spectrometer (Finnigan MAT). Melting points were recorded on a PL-DSC (Polymer Laboratories) machine. Absorption and emission spectra were recorded on a Shimadzu UV-1601 spectrometer and a Perkin-Elmer LS 50 luminescence spectrometer, respectively. Single-crystal X-ray diffraction data were collected on a Kappa CCD diffractometer using Mo Kα radiation ($\lambda = 0.7107$ Å).

All optical measurements were performed in analytical grade solvents. The effect of residual water in the solvents and materials was tested and found to be negligible. Nitrate hydrate salts of the relevant metal ions were used for all the binding experiments. All reagents and solvents were used as received unless noted. Anhydrous solvents were obtained using standard methods.

II.b. Materials. 1-Ethoxymethyl-1H-imidazole, 2. A solution of chloromethylethyl ether (11.2 g, 140 mmol) and triethylamine (25 g, 175 mmol) in 50 mL of dry THF was added dropwise over a period of 30 min to a solution of imidazole, **1**, (10 g, 147 mmol) in 400 mL of dry THF under argon at 0 °C. After the addition was completed, the mixture was stirred at room temperature for several hours. Filtration of the white solid and evaporation of the solvent yielded a yellow oil. Distillation of the oil (80−90 °C, 0.2 Torr) yielded 15.7 g (85%) of **2** as a colorless liquid.

MS (CI): m/z 127 $(M + H)^+$. ^{1}H NMR ($CDCl_3$): δ 7.567 (s, 1H), 7.06 (d, 2H), 5.25 (s, 2H), 3.46 (q, 2H), 1.18 (t, 3H). ^{13}C NMR ($CDCl_3$): δ 136.7, 129.1, 118.3, 75.5, 63.7, 14.1.

Naphthalene-1,8-dicarboxylic Acid Dimethyl Ester, 3. 1,8-Naphthalene anhydride (10 g, 50.3 mmol) was added to an aqueous KOH solution (10 g, 178 mmol, in 300 mL), and the mixture was refluxed overnight. The reaction mixture was then cooled to room temperature, extracted with three portions of dichloromethane (50 mL), and the aqueous phase was poured into concentrated HCl (100 mL) at 0 °C. The solid product was filtered, washed with water, and dried under reduced pressure to produce naphthalene-1,8-dicarboxylic acid in a 91% yield (10 g).

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mp (DSC): 99.01 °C. ^{1}H NMR (DMSO-d_6): δ 8.13 (d, 2H), 8.01 (d, 1H), 7.94 (d, 2H), 7.62 (t, 2H). ^{13}C NMR (DMSO-d_6): δ 193.99, 159.94, 158.44, 157.04, 156.33, 155.76, 153.636, 152.07, 149.9.

Naphthalene-1,8-dicarboxylic acid (5 g, 23.1 mmol) was dissolved in an aqueous sodium carbonate solution (6 g, 56.6 mmol, in 50 mL) and heated to 40 °C. After the addition of dimethyl sulfate (14.1 mL, 150 mmol), the mixture was stirred at 40 °C for another 2 h. The mixture was then brought to room temperature, and the solid product was filtered, washed with water, and dried, giving **3** in an 81% yield (white solid, 4.6 g).

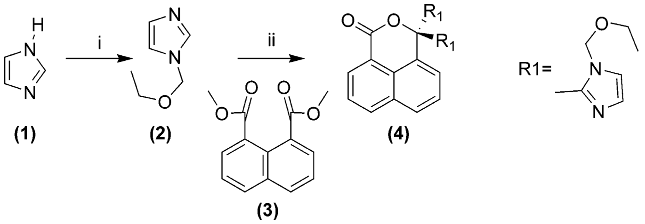
mp (DSC): 100 °C. MS (CI): *m/z* 244. ^{1}H NMR (CDCl$_3$): δ 8.00 (dd, 4H), 7.56 (t, 2H), 3.89 (s, 6H). ^{13}C NMR (CDCl$_3$): δ 169, 134.23, 132.29, 130, 129.78, 125.16, 51.9.

3,3-Bis-(1-ethoxymethyl-1H-imidazol-2-yl)-3H-benzo[de]isochromen-1-one, 4. A solution of *n*-butyllithium in hexane (1.6 M, 12.5 mL, 20 mmol) was added slowly to a solution of 1-ethoxymethyl-1H-imidazole, **2**, (2.54 g, 20 mmol) in 40 mL of dry THF at −78 °C under an inert atmosphere. The mixture was stirred for 10 min at −78 °C, then it was warmed to −30 °C for 10 min. At this point, the mixture was cooled again to −78 °C, and a solution of naphthalene-1,8-dicarboxylic acid dimethyl ester, **3**, (2.44 g, 10 mmol) in dry THF (40 mL) was added, while the temperature was held below −65 °C. The mixture was stirred for 90 min at −78 °C; then it was allowed to reach room temperature and was stirred for additional 12 h at room temperature. Water (50 mL) and diethyl ether (50 mL) were then added, and the phases were separated. The aqueous phase was extracted with three portions of dichloromethane (50 mL), and the combined organic phases were dried over anhydrous sodium sulfate. After the solvent was removed, the resulting oil was column chromatographed over alumina using 5% methanol in dichloromethane as the eluent. The crude, a yellowish solid, was recrystallized from diethyl ether, giving **4** in a 79% yield (yellowish solid, 3.4 g). mp (DSC): 152.6 °C. MS (CI): *m/z* 433 (M^{+}). ^{1}H NMR (CDCl$_3$): δ 8.41 (d,1H), 8.20 (d, 1H), 7.98 (d, 1H), 7.67 (t, 1H), 7.60 (t, 1H), 7.22 (m, 1H), 7.18 (s,2H), 6.96 (s, 2H), 5.40 (d, 2H), 5.19 (d, 2H), 3.30 (q, 4H), 0.90 (t, 6H). ^{13}C NMR (CDCl$_3$): δ 145, 134, 132, 130, 128.8, 128.5, 127.6, 127.2, 126.4, 126.1, 122, 119, 77, 64, 14.

II.c. X-ray Crystallography. Crystallographic Data for 4. The crystallographic data for **4** are as follows: $C_{24}H_{24}N_4O_4$, M_r = 432.47, a = 8.3160(1) Å, b = 22.7657(3) Å, c=11.5031(7) Å, β = 98.854(2)°, Z = 4, d_{calcd} = 1.335 g cm^{-3}, V = 2151.8(1) Å^3, monoclinic, space group $P2_1/n$. Data for a colorless crystal with dimensions of 0.32 × 0.24 × 0.15 mm were collected at 150(2) K on a Nonius KappaCCD diffractometer using Mo Kα radiation (λ = 0.71073 Å). The following data were collected with subsequent φ and ω scans (363 frames, rotation per frame 1.5°, exposure per frame 180 s): 27 163 reflections collected, 3062 unique, 2628 above threshold [$I > 2\sigma(I)$]. Final R1 = 0.038 (0.050 for all reflections); wR2 = 0.085 (0.089 for all reflections).

Crystallographic Data for the Zn^{II}·4·2Cl^{-} Complex. The crystallographic data are as follows: $C_{24}H_{24}N_4O_4CL_2Zn$, M_r = 568.74, a = 15.5018(5) Å, b = 18.5910(4) Å, c = 19.7899(6) Å, α = 89.924(2)°, β = 70.860(1)°, γ = 73.456(2)°, Z = 8, d_{calcd} = 1.470 g cm^{-3}, V = 5138.3(3) Å^3, triclinic, space group $P\bar{1}$. Data for a colorless crystal with dimensions of 0.20 × 0.20 × 0.10 mm were collected at 150(2) K on a Nonius KappaCCD diffractometer using Mo Kα radiation (λ = 0.71073 Å). The following data were collected with subsequent φ and ω scans (212 frames, rotation per frame 1.5°, exposure per frame 450 s): 41 830 reflections collected, 14 421 unique, 10 447 above threshold [$I > 2\sigma(I)$]. Final R1 = 0.064 (0.100 for all reflections); wR2 = 0.093 (0.103 for all reflections).

Scheme 2 ^{a}



^{a} (i) Et$_3$N, chloromethylethyl ether, 0 °C−RT, 85%; (ii) *n*-butyl lithium, naphthalene-1,8-dicarboxylic acid dimethyl ester, −60 °C−RT, 85%.

The diffractometer control program was Collect (Nonius B. V. 1998); the unit cell parameters and the data reduction were calculated with Denzo and Scalepak (Otwinowski & Minor, 1997), and the structures were solved by direct methods SHELXS-97 (Sheldrick, 1990) and refined on F^2 by full-matrix least-squares with SHELXL-97 (Sheldrick, 1997).

CCDC contains the supplementary crystallographic data (607612 and 607613) for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44-1223/336-033. E-mail: deposit@ccdc.cam.ac.uk.).

III.Results and Discussion

III.a. Material Synthesis and Characterization. 3-(3-Ethoxymethyl-1H-imidazol-2-yl)-3-(1-ethoxymethyl-1H-imidazol-2-yl)-3H-benzo[de]isochromen-1-one, **4**, was prepared according to Scheme 2. Imidazole, **1**, was N-protected using chloromethylethyl ether in the presence of triethylamine; the reaction yielded 1-ethoxymethyl-1H-imidazole, **2**, in an 85% yield. This product was then lithiated at the 2-position using *n*-butyllithium and reacted with naphthalene-1,8-dicarboxylic acid dimethyl ester, **3**, at low temperature to produce the target benzo[de]isochromen-1-one derivative **4** in an 85% yield.

3-(3-Ethoxymethyl-1H-imidazol-2-yl)-3-(1-ethoxymethyl-1H-imidazol-2-yl)-3H-benzo[de]isochromen-1-one, **4**, readily dissolves in a large variety of organic solvents producing transparent solutions with only a very faint fluorescence. Figure 1 depicts the absorption and emission spectra of **4** in acetonitrile. Solutions of **4** are found to be very sensitive to the presence of even submicromolar traces of zinc ions, Figure 2. As can be seen in Figure 2, the addition of even minute amounts of zinc ions results in an increase in the luminescence of **4** with saturation at at 1:1 Zn^{II}/**4** ratio. Under saturation conditions, the luminescence of **4** in acetonitrile is ca. 900 times higher than that in the absence of zinc ions. In contrast, the absorption spectrum of **4** is practically unaffected by the presence of the zinc ions. The combination of a guest-independent absorption spectrum and a guest-dependent luminescence spectrum is indicative of a PET-based luminophore-sensing system.

The affinity of **4** toward other metal ions, such as Cd^{2+}, Mg^{2+}, and Ca^{2+}, is significantly lower than that for Zn^{2+}, as can be seen in Figure 3 and Table 1. Additionally, the fluorescence intensity of **4** was found to be practically

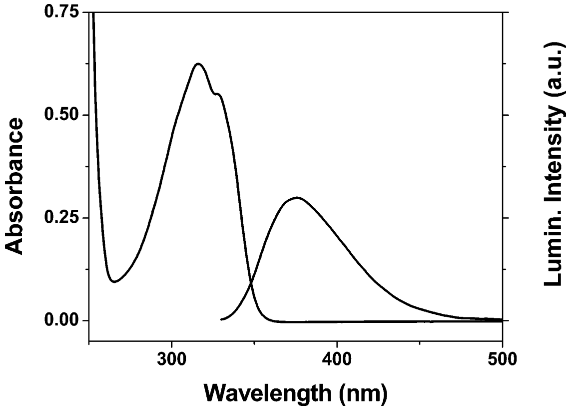


Figure 1. Absorption and emission spectra ($\lambda_{ex} = 329$ nm) of a solution of 1×10^{-5} M 3-(3-ethoxymethyl-1H-imidazol-2-yl)-3-(1-ethoxymethyl-1H-imidazol-2-yl)-3H-benzo[de]isochromen-1-one, **4**, in acetonitrile.

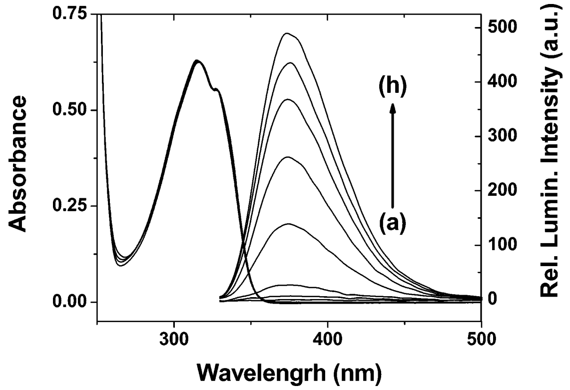


Figure 2. Absorption and emission ($\lambda_{ex} = 329$ nm) spectra of a solution of 1×10^{-5} M 3-(3-ethoxymethyl-1H-imidazol-2-yl)-3-(1-ethoxymethyl-1H-imidazol-2-yl)-3H-benzo[de]isochromen-1-one, **4**, in acetonitrile in the presence of different concentrations of $Zn^{II}(NO_3)_2$: (a) 0, (b) 9.99×10^{-8}, (c) 4.98×10^{-7}, (d) 9.90×10^{-7}, (e) 2.47×10^{-6}, (f) 4.93×10^{-6}, (g) 7.37×10^{-6}, and (h) 9.8×10^{-6} M.

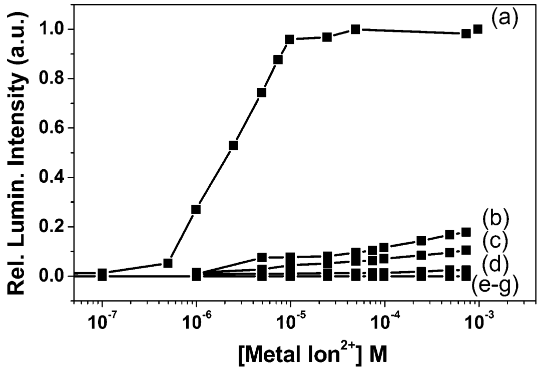


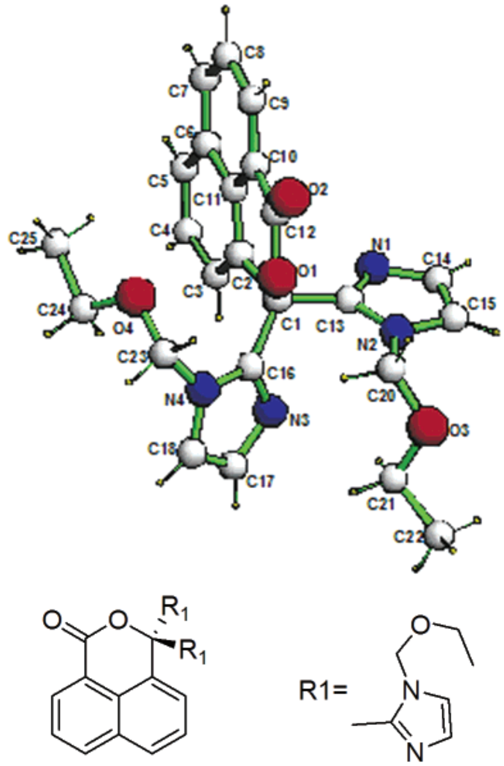
Figure 3. Relative emission intensities ($\lambda_{ex} = 329$ nm) of a solution of a 1×10^{-5} M solution of 3-(3-ethoxymethyl-1H-imidazol-2-yl)-3-(1-ethoxymethyl-1H-imidazol-2-yl)-3H-benzo[de]isochromen-1-one, **4**, in acetonitrile in the presence of different concentrations of different metal ions: (a) $Zn^{II}(NO_3)_2$, (b) $Cd^{II}(NO_3)_2$, (c) $Mg^{II}(NO_3)_2$, (d) $Ca^{II}(NO_3)_2$, (e) $Li^{I}NO_3$, (f) $Na^{I}NO_3$, and (g) $K^{I}NO_3$.

independent of the presence of Li^+, Na^+, and K^+, at least up to millimolar concentrations. The weaker effect of these ions is indicative of the reduced affinity of **4** toward those ions. Table 1 depicts the different association constants that were calculated from the metal induced gain in luminescence.

Table 1. Association Constants between **4** and Different Metal Ions[a]

ion	K_a (M^{-1})	ion	K_a (M^{-1})
Zn^{2+}	>3 000 000	Li^+	<100
Cd^{2+}	30 000	Na^+	<100
Mg^{2+}	7000	K^+	<100
Ca^{2+}	5000		

[a] K_a values are provided for the association in acetonitrile, $T = 298 \pm 2$ K. The error for all K_a values is estimated to be ±15%.



(4)

Figure 4. Molecular structure and atom numbering of the free base of **4** in the solid state.

III.b. Crystal Structures. The molecular structure of the free base of **4** in the crystal is depicted in Figure 4. As can be seen from the figure, the two 2-(1-ethoxymethyl)-imidazole subunits adopt different conformations with respect to the 3H-benzo[de]isochromen-1-one skeleton. The ethoxymethyl substituent of the first imidazole group is folded in a manner in which the zigzag chain is almost parallel to the 3H-benzo[de]isochromen-1-one plane, and this brings it into close contact with the naphthalene skeleton. The oxygen atom of the ethoxymethyl group is relatively close to the centroid of one of the C2, C3, C4, C5, C6, C11 rings of the naphthalene skeleton, $d = 3.923(3)$ Å, as well as one of the hydrogen atoms of the terminal methyl group, $d = 2.85$ Å. The lone pair electrons of this imidazole ring are far from the π-electron cloud of the naphthalene group.

The ethoxymethyl substituent of the second imidazole group is positioned on the nitrogen atom of the imidazole ring that is pointing to the opposite direction, far away from the naphthalene group. The lone pair electrons of the second imidazole ring point toward the π-electron cloud of the C2, C3, C4, C5, C6, C11 ring; the distance of the N atom to the center of this ring, d, is 3.593(2) Å, and the imidazole ring is perpendicular to the naphthalene skeleton (dihedral angle = 89.43(5)°), Figure 5. Additional information regarding the crystal structure and molecular packing of **4** can be obtained

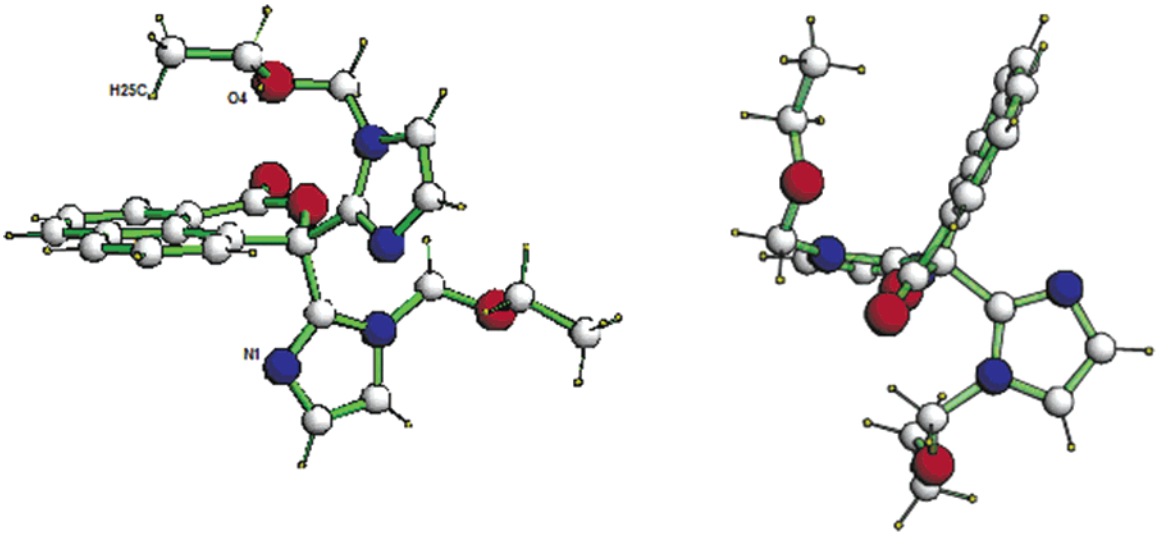


Figure 5. Conformation and orientation of one imidazole group with respect to the 3H-benzo[de]isochromen-1-one skeleton.

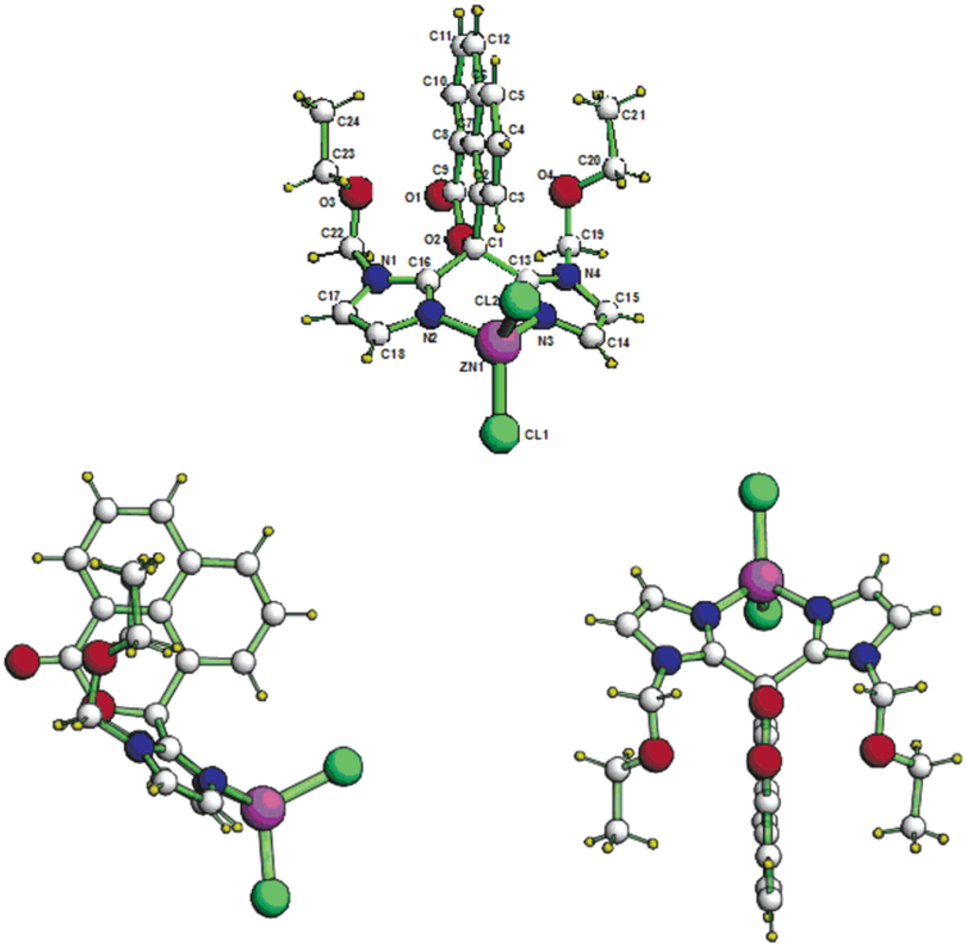


Figure 6. Top and side views of the X-ray structure of the $\mathbf{Zn^{II} \cdot 4 \cdot 2Cl^-}$ complex (molecule 1).

from the Cambridge Crystallographic Data Centre as described in the Experimental Section.

When the zinc ion is bound, the two imidazole rings become engaged in new $Zn^{II} \cdots N_{imidazole}$ coordinative bonds. Four independent complex molecules were found in the asymmetric unit. The bond lengths, bond angles, and conformation of each complex molecule are very similar so only one of them is shown in Figure 6. The complex exhibits pseudo-planar symmetry. Both lone pair electrons of the oxygen atoms of the methylethyl ether protective group are in close contact with the 3H-benzo[de]isochromen-1-one plane (2.222(6)−2.384(7) Å), and one of the H-atoms of the terminal methyl groups points toward the center of one of the naphthalene rings (the distance of the methyl hydrogen to the 3H-benzo[de]isochromen-1-one plane varies from 2.18 to 2.52 Å). The two imidazole rings flip to an orientation

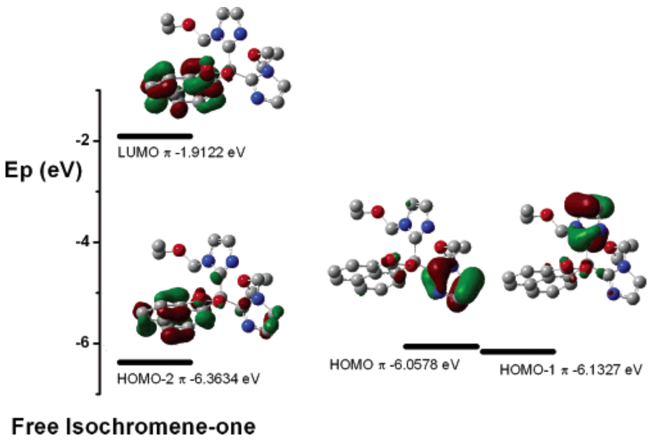


Figure 7. Orbital energy diagrams for **4** (Gaussian 98[13] software package, B3LYP/6-31g(d)). The dominant nature of each orbital and its energy in electronvolts is provided.

that is almost orthogonal (dihedral angle = 97.4(2)−109.3(2)°) to the naphthaleneimide moiety. The dihedral angles between the imidazole rings in the four complex molecules are 142.3(2), 147.6(2), 155.3(3), and 155.6(2)°.

III.c. Electronic Energy Calculations and Orbital Energy Diagrams. With the aim of better understanding the new PET system and because **4** is a new type of PET sensor, based on a bisimidazole quencher and binding site, we calculated an orbital energy level diagram for the free host and its Zn^{II} complex (Gaussian 98).[13] First, the structures of the host, **4**, and its Zn^{2+} complex were optimized at the B3LYP/6-31g(d) level.[14] In the next step, the energies of the LUMO, HOMO, HOMO−1, HOMO−2, and any other relevant orbital of the energy-minimized systems were extracted from the calculations. The energy levels of the different systems, including all relevant orbitals, are presented in Figures 7 and 8 for the free host, **4**, and its zinc complex, **Zn^{II}·4·2Cl$^-$**, respectively.

As can be seen in Figure 7, the two π-orbitals of the two imidazole rings are located between the two orbitals that participate in photoexcitation and photoluminescence. In contrast, the lone pairs of the nitrogen atoms of the imidazole rings are at a lower energy than the HOMO−2. The presence of orbitals in the gap between the two orbitals that participate in photoexcitation and photoluminescence processes is indicative of a PET system. This explains the very low luminescence efficiency that is found for the free host, **4**. In the Zn^{II} complex, both the HOMO and LUMO are π-orbitals of the chromophore that participates in the photoexcitation and photoluminescence processes. In the complex, the π-orbitals of the imidazole rings are located at HOMO−2 and HOMO−3.

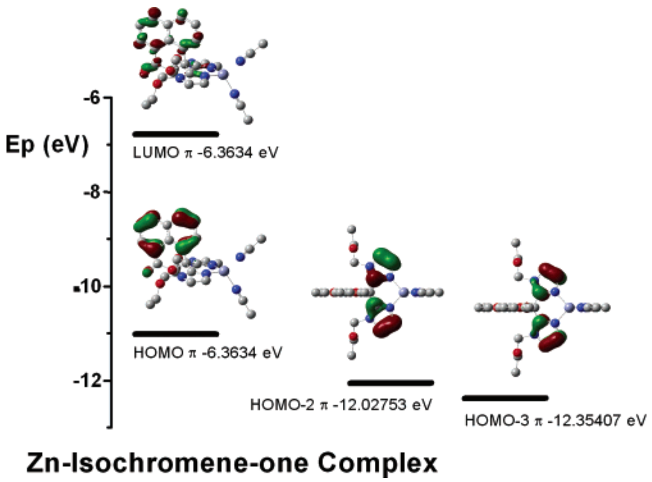


Figure 8. Orbital energy diagrams for **Zn^{II}·4·2Cl$^-$** (Gaussian 98[13] software package, B3LYP/6-31g(d)). The dominant nature of each orbital and its energy in electronvolts is provided.

IV. Conclusions

A new bisimidazole-based PET system, 3-(3-ethoxymethyl-1H-imidazol-2-yl)-3-(1-ethoxymethyl-1H-imidazol-2-yl)-3H-benzo[de]isochromen-1-one, **4**, was prepared and characterized in terms of its affinity to different metal ions. The new material shows a clear preference toward Zn^{II} ions and **Zn^{II}·4** is found to be ca. 900 times more fluorescent than free host **4**.

The new bisimidazole PET system and its zinc complex were characterized in terms of their crystal structure and orbital energy diagrams.

A model is suggested to rationalize the results, in which the π-systems of the two imidazole rings of free **4** serve as quenchers for the excited state of the isochromene-one luminophore. In the **Zn^{II}·4** complex, the π-systems of the two imidazole rings are stabilized and can no longer serve as quenchers to the excited state of the luminophore. Therefore, the luminescence of **4** is enhanced upon binding of Zn^{II} Ions.

Ligand **4** is not water soluble and does not show the same strong affinity toward metal ions in aqueous solutions. Nevertheless, improved water soluble systems are currently under investigation and will be reported elsewhere.

Acknowledgment. This research was supported by the Israel Science Foundation (ISF).

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