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Tetrahedron Letters 49 (2008) 772–776

Tetrahedron Letters

Unprecedented four-way-output molecular response system based on biphenyl-2,2′-diyldiacridiniums: induction of axial chirality through intramolecular hydrogen bonds between chiral amide groups

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Received 6 November 2007; revised 27 November 2007; accepted 29 November 2007

Abstract

Upon the attachment of *N*-(*R*)-2-phenylethylamide moieties to the acridinium units of the title dication, intramolecular hydrogen bonds induce a diastereomeric preference in terms of axial chirality (70% de at −40 °C in CH_2Cl_2). Thus, external stimuli induce not only UV–vis and fluorescence spectra changes but also changes in the CD and fluorescence-detected CD (FDCD) spectra, realizing unprecedented four-way-output molecular response systems.

Keywords: Molecular response systems; Dynamic redox system; Hydrogen bond; Amide; Chirality; Electrochiroptics; Fluorescence; CD; FDCD

While multi-input–multi-output response systems[1] are rare, they have attracted considerable attention from the viewpoint of potential applications in molecular sensing. Since multi-input systems are prototypes of molecular-level logic operators,[2] the functional addition of a multi-output response would endow such systems with the ability to act as parallel operating logic elements ('molecular CPU'[3]). The redox pairs of **1**,**2**/**1**,$\mathbf{2}^{2+}$ with point chiralities have been designed here (Scheme 1) as new components of electrochiroptical response systems,[4] by which an electrochemical input is transduced into two kinds of output (UV–vis and CD). By exploiting the temperature- and solvent-dependence of the interconvertible chiral sense of helicity and axial chirality, we have succeeded in constructing a three-way-input molecular response system. Because we could detect four kinds of spectral changes, thanks to the fluorophoric nature of the dicationic species, the present molecules can serve as unprecedented four-way-output response system. It is also noteworthy that the redox reactions are accompanied by C–C bond formation/cleavage ('dynamic redox properties'),[5] so that they exhibit high electrochemical bistability.

We have previously shown[6] that biphenyl-2,2′-diylbis(10-methylacridinium) $\mathbf{3}^{2+}$ consists of a new entry of two-way-output (UV–vis and fluorescence) response system due to the orange-colored acridinium chromophore that emits green fluorescence. Upon 2e-reduction, dication $\mathbf{3}^{2+}$ is transformed into the colorless and non-fluorescent dihydrophenanthrene **3**. Their skeletal structures are also interesting in terms of molecular chirality: each has an asymmetric element; that is, helicity in the neutral electron donor **3** and axial chirality in the electron-accepting dication $\mathbf{3}^{2+}$. Although they are configurationally too labile to be resolved, chiroptical properties such as circular dichroism (CD) become available as outputs by biasing

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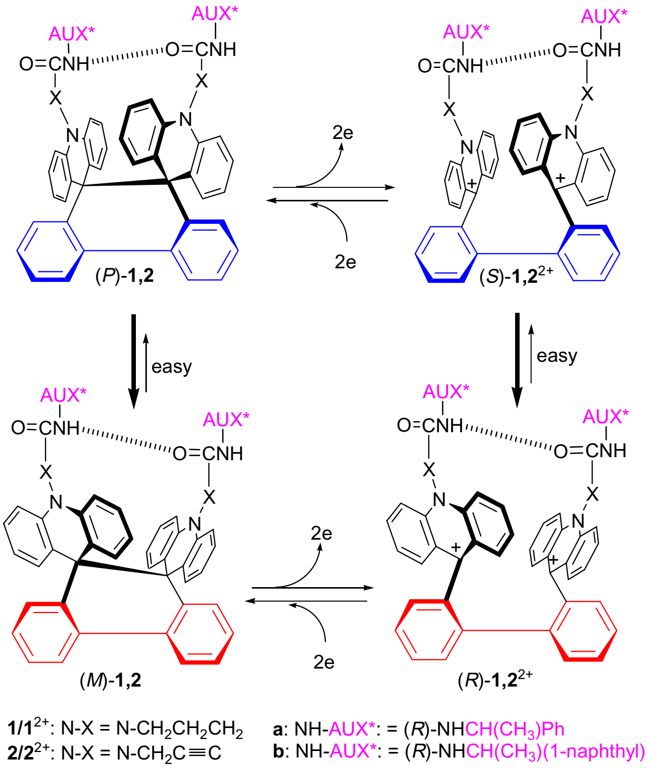
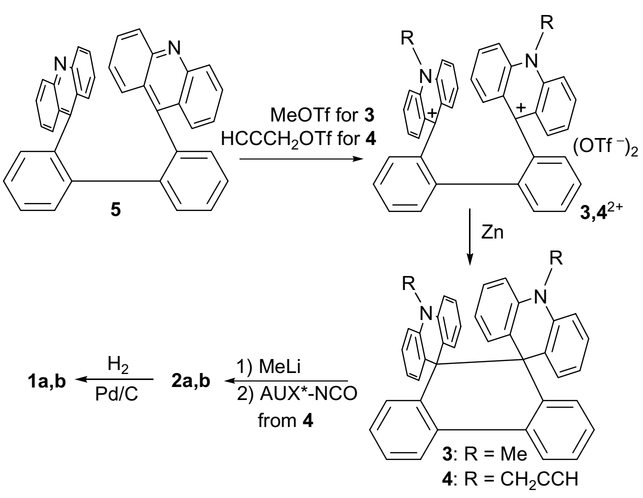
doi:10.1016/j.tetlet.2007.11.179



Scheme 1.

the preference for chiral conformers. Fluorescence-detected CD (FDCD)[7] may also serve as a highly sensitive technique for monitoring chiral modulation by external stimuli. We envisaged that the easily convertible chiral sense in **3** and **3**$^{2+}$ could be modified to prefer one handedness if suitable point chiralities are attached to the molecule. Although chiral auxiliaries of simple asymmetric centers (AUX*) only induce CD signals ($\Delta\varepsilon < 1$) that are too weak to be detected as an output, the diastereomeric preference caused by AUX* would result in strong chiroptical signals, thanks to an exciton-coupling mechanism in helical or axially chiral skeletons (‘chiroptical enhancement’[8]).



Scheme 2.

Since the diastereomeric ratio is also affected by external stimuli other than an electric potential, chirally modified title dications are promising candidates to serve as multi-input response systems. To attain a high diastereomeric preference in terms of the skeletal chiral sense, the redox pairs of **1a**,**b**/**1a**,**b**$^{2+}$, which possess chiral amide groups (AUX*-NHCO–) on acridinium nitrogens, were designed. (*R*)-1-Phenylethylamino-(**a**) or (*R*)-1-(1-naphthyl)ethylamino-(**b**) groups are chosen as AUX*–NH– units. By attaching proper spacer groups such as $CH_2CH_2CH_2$, intramolecular hydrogen bonds would be formed between those amide groups, which would bias the preference for the direction of skewing to induce chiroptical properties. Here we report the preparation, redox properties and response behavior of novel redox systems designed above

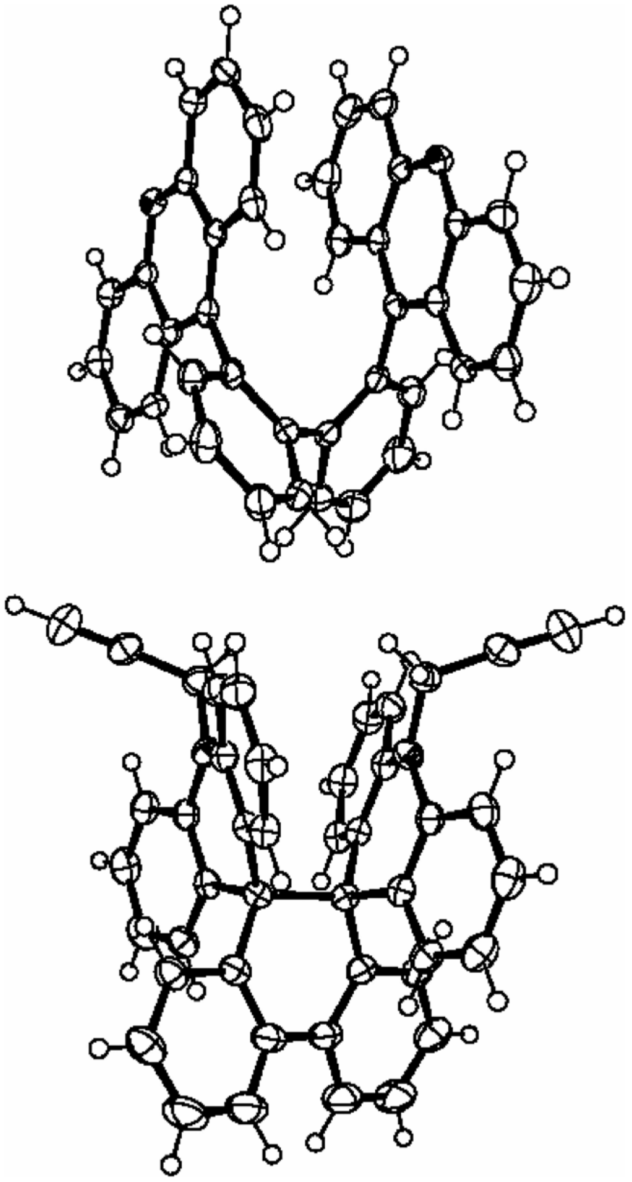


Fig. 1. X-ray structures of **5** (upper) and **4** (lower) measured at −120 °C.

(**1a**,**b**/**1a**,**b**$^{2+}$) as well as **2a**,**b**/**2a**,**b**$^{2+}$ possessing $CH_2C{\equiv}C$ spacers.

2,2′-Dilithiobiphenyl was generated by the reaction of 2,2′-diiodobiphenyl and BuLi, and then reacted with 10-methoxyethoxymethyl(MEM)-9-acridone.[9] Acidic workup induced the removal of MEM groups, and successive dehydration gave biphenyl-2,2′-diylbis(9-acridine) **5** in 53% yield (Scheme 2). According to an X-ray analysis,[10] **5** adopts the skewed *syn*-form [twisting angle of biphenyl: 57.3(1)°] with two acridine units partially overlapped in parallel (interplanar distance: 3.17 Å; dihedral angle: 4.3°) (Fig. 1a). Treatment of **5** with methyl trifluoromethanesulfonate (MeOTf) gave 10,10′-dimethyl dication **3**$^{2+}$ as the $(OTf^-)_2$ salt, with properties that are identical to those of the $(BF_4^-)_2$ salt prepared previously in lower yield via the leuco base.[6] Similarly, 10,10′-dipropargyl dication **4**$^{2+}$ was obtained by treatment of **5** with propargyl trifluoromethanesulfonate in 80% yield, showing that diacridine **5** can be used as a versatile synthon to give a series of biphenyl-based bis(10-alkylacridinium)s. Since the dications also prefer the skewed *syn*-form[4e,5,11] as in **5**, the two amide groups in **1a**,**b**$^{2+}$ would have a chance to interact intramolecularly through the hydrogen bond in less-polar solvents. Upon the reduction of **4**$^{2+}$ with Zn powder, a long C–C bond [1.634(3) Å][10] was made between C9 carbons of acridiniums to form the electron donor **4** in 89% yield, in which non-interacting propargyl groups are directed outward (Fig. 1b).

Upon double deprotonation at the two terminal alkyne moieties by MeLi followed by reaction with chiral isocyanates (AUX*–N=C=O), diamides **2a**,**b** were obtained in respective yields of 94% and 54%.[12] The desired electron donors **1a**,**b** were prepared by the hydrogenation (10% Pd/C) of triple bonds in **2a**,**b** in respective yields of 72% and 57%. The newly formed dispiro electron donors **1a**,**b** [E^{ox}: +0.29 and +0.31 V vs SCE in MeCN, respectively] and **2a**,**b** [+0.46; +0.48 V] are stable colorless solids and can be smoothly transformed into the corresponding

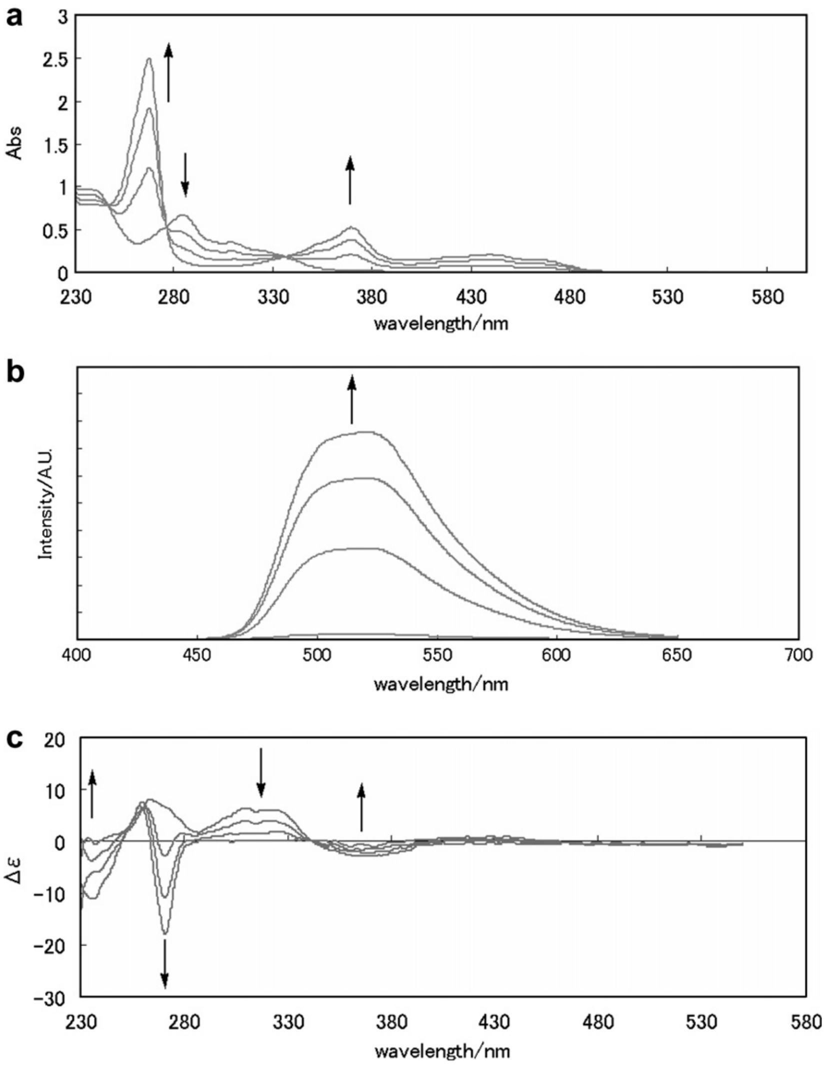


Fig. 2. Changes in (a) UV–vis, (b) fluorescence, and (c) CD spectra upon constant-current electrochemical oxidation (23 micro A) of **1a** (2.2×10^{-5} M, 3.5 mL) to **1a**$^{2+}$ in CH_2Cl_2 containing 0.05 M $^{n}Bu_4NBF_4$ (every 5 min). The value of Δε is defined as $\varepsilon_L - \varepsilon_D$ and shown in the unit of $M^{-1}\,cm^{-1}$.

dications **1a**,**b**$^{2+}$ and **2a**,**b**$^{2+}$ upon treatment with 2 equiv of $(4\text{-BrC}_6\text{H}_4)_3\text{N}^{+\cdot}\text{SbCl}_6^-$ [isolated yields of orange-colored $(\text{SbCl}_6^-)_2$ salts: 85–98%]. On the other hand, the starting electron donors were regenerated upon the reduction of electron-accepting dicationic salts **1a**,**b**$^{2+}(\text{SbCl}_6^-)_2$ [E^{red}: −0.20 and −0.22 V vs SCE, respectively] and **2a**,**b**$^{2+}(\text{SbCl}_6^-)_2$ [−0.10; −0.08 V] with Zn powder (isolated yields: 91–100%). This high-yield interconversion indicates that **1a**,**b**/**1a**,**b**$^{2+}$ and **2a**,**b**/**2a**,**b**$^{2+}$ can be considered 'reversible' redox pairs despite their microscopic irreversibility due to C–C bond formation/cleavage upon electron transfer. The greater positive values (less negative values) of redox potentials for **2a**,**b**/**2a**,**b**$^{2+}$ than for **1a**,**b**/**1a**,**b**$^{2+}$ are due to the electron-withdrawing properties of the propargyl groups.

In the CD spectra of dications **1a,b**$^{2+}$ in CH_2Cl_2, negative couplets were observed at around 265 nm, and these originated from exciton-coupling[13] of the characteristic absorption of 9-aryl-10-alkylacridiniums. The CD amplitudes ($A \equiv \Delta\varepsilon_{\text{long}} - \Delta\varepsilon_{\text{short}}$) of −18 for **1a**$^{2+}$ (Δε −13.5 at 271 nm, +4.0 at 259 nm) and −29 for **1b**$^{2+}$ (−10.6 at 273 nm, +18.1 at 262 nm) are strong enough for their use as electrochiroptical response systems. According to the ^{1}H NMR analyses in CD_2Cl_2 at −40 °C, the chiral sense of axial chirality is biased with a diastereomeric excess of 70% for **1a**$^{2+}$ and 75% for **1b**$^{2+}$. On the other hand, **2a**,**b**$^{2+}$, which have propargyl spacers, exhibit weaker CD signals. Such differences can be accounted for by considering that the rigid propargyl spacers in **2a**,**b**$^{2+}$ may prevent effective intramolecular hydrogen bonding by directing the amide groups outward. In terms of the AUX* moiety, a phenylethyl group (**a**) is much more suitable than a naphthylethyl group (**b**) for pursuing a multi-output response system since the electron-donating naphthalene core in AUX* completely quenches the emission from acridinium units in **1**,**2b**$^{2+}$.

Based on the above considerations, the redox pair of **1a**/**1a**$^{2+}$ was chosen to study the electrochemical response. Figure 2a shows the changes in UV–vis spectra upon electrochemical oxidation of **1a** in CH_2Cl_2. The colorless solution gradually turned to orange, and the isosbestic points indicate clean conversion as well as a negligible steady-state concentration of the intermediate cation-radical species. Though the fluorescence quantum yield of **1a**$^{2+}$ ($\Phi_{\text{F}} = 0.08$ in CH_2Cl_2) is slightly lower than that of dimethyl derivative **3**$^{2+}$, it is high enough to use its fluorescence as an output signal, as shown in Figure 2b. Furthermore, the exciton-type CD couplet gradually grows at around 265 nm upon the electrolysis of **1a** to **1a**$^{2+}$ in CH_2Cl_2 (Fig. 2c). This is a new successful demonstration of three-way-output in response to electrochemical input.[4g]

The intramolecular hydrogen bond between two chiral amide groups is responsible for inducing the observed diastereomeric preference since the CD signals of **1a**$^{2+}$ show a drastic decrease when the solvent composition is changed from pure CH_2Cl_2 to a CH_2Cl_2–MeCN mixture; the latter polar solvent can break hydrogen bonds (Fig. 3a). A similar change was also observed in **1b**$^{2+}$ with naphthylethyl chiral auxiliaries. If we take advantage of the high sensitivity of the FDCD technique,[14] changes with solvent-polarity can be detected even with the use of a diluted solution of 10^{-6} M (Fig. 3b). Furthermore, the CD signals of **1a**$^{2+}$ exhibit noticeable temperature-dependence: a 15% increase in Δε upon cooling the solution from +20 °C to −20 °C in CH_2Cl_2. In this way, three kinds of external stimuli (electric potential, solvent-polarity, heat) can be transduced into the chiroptical response of the present system. This work presents a prototype for a three-way-input-four-way-output molecular response system. Studies on other multi-input–multi-output response systems[15] are now in progress by applying this approach based on the transmission of point chirality to axial chirality or helicity.[16]

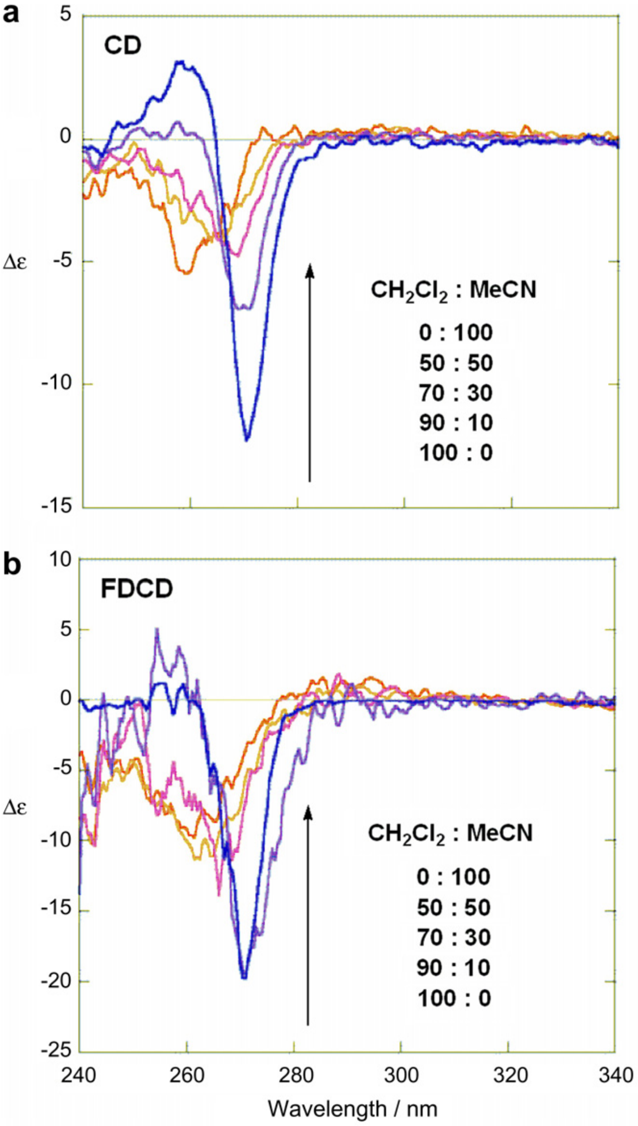


Fig. 3. Solvent-composition dependence in (a) CD ($1.2\text{–}1.5 \times 10^{-5}$ M) and (b) FDCD spectra ($1.3\text{–}1.7 \times 10^{-6}$ M) of **1a**$^{2+}$ $(\text{OTf}^-)_2$ at 25 °C: CH_2Cl_2–MeCN 0:100 (red), 50:50 (orange), 70:30 (pink), 90:10 (purple), and 100:0 (blue). The negative Cotton effect at around 260 nm in pure MeCN is assigned to the isolated phenylethylamide moiety. The value of Δε is defined as $\varepsilon_{\text{L}} - \varepsilon_{\text{D}}$ and shown in the unit of $\text{M}^{-1}\,\text{cm}^{-1}$.

Acknowledgments

National Research Institute of Brewing is gratefully acknowledged for use of the FDCD instrument. This work was partly supported by the Global COE Program (Project No. B01: Catalysis as the Basis for Innovation in Materials Science) from the Ministry of Education, Science and Technology, Japan.

Supplementary data

Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 650120, 650121, and 666230. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. Spectral data and synthetic procedures of the new compounds and X-ray structure of **1c** (Fig. S1). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007. 11.179.

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10. Crystal data are as follows: **4**·benzene$_6$ solvate: MF $C_{44}H_{30}N_2(C_6H_6)_6$, FW 1055.41, orthorhombic *P*ccn (No. 56), $a = 11.899$ (1), $b = 17.125$ (2), $c = 29.198$ (3) Å, $V = 5949.5$ (9) Å^3, $\rho(Z = 4) = 1.178$ g cm^{-3}, $T = 153$ K, $R = 9.0\%$. CCDC 650120. **5**·chloroform solvate: MF $C_{38}H_{24}N_2(CHCl_3)$, FW 628.00, monoclinic $P2_1/c$ (No. 14), $a = 10.594$ (3), $b = 15.113$ (5), $c = 18.437$ (6) Å, $\beta = 91.729$ (8)°, $V = 2950$ (1) Å^3, $\rho(Z = 4) = 1.414$ g cm^{-3}, $T = 153$ K, $R = 4.8\%$. CCDC 650121. **1c**·ethyl acetate solvate: MF $(C_{60}H_{52}N_4O_2)_2(C_4H_8O_2)_3$, FW 1986.51, triclinic $P\bar{1}$ (No. 2), $a = 15.970$ (7), $b = 18.706$ (7), $c = 19.090$ (6) Å, $\alpha = 72.440$ (16), $\beta = 76.540$ (15), $\gamma = 90.01$ (2)°, $V = 5273$ (3) Å^3, $\rho(Z = 2) = 1.251$ g cm^{-3}, $T = 153$ K, $R = 16.2\%$. CCDC 666230.
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