Self-Assembled Dimers

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Water and Hydrogen Halides Serve the Same Structural Role in a Series of 2+2 Hydrogen-Bonded Dimers Based on 2,6-Bis(2-anilinoethynyl)pyridine Sulfonamide Receptors**

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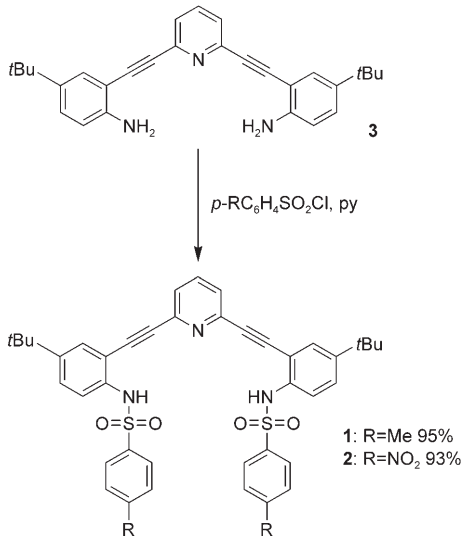
The complex hydrogen-bonding interactions of the water molecule are remarkable: water plays a vital role in a number of systems ranging from the formation of hydrogen-bonded water oligomers[1] to the increased conformational stability of proteins[2] and the crucial synergistic hydrogen bonds formed in enzymatic[3] or biomimetic[4] active sites. In many cases these hydrogen bonds dictate both structure and function. In supramolecular chemistry, synergistic hydrogen bonding between water and organic molecules has helped to stabilize vase-like conformations of hosts for organic molecules[5] and to induce the formation of intricate hexameric nanoscale capsules stitched together with the aid of eight water molecules.[6] In both cases these hosts can be stabilized in wet organic or purely aqueous solvents.[7] Anions, on the other hand, tend not to share the structural hydrogen-bonding diversity of water, in part as a result of the weak basicity of anions and often because of a lack of directionality in their hydrogen-bond formation.[8,9] Nevertheless, there is an emerging use of anions as directing elements in self-assembly reactions. Notable examples include a double-stranded helix wrapped around two sulfate anions;[10] catenanes and other structures templated by the formation of hydrogen bonds to anions;[11] and supramolecular dimers, oligomers, and polymers linked together by anions.[12] Herein we report new receptors based on a 2,6-bis(2-anilinoethynyl)pyridine scaffold that surprisingly form 2+2 dimers with either water, halides, or both, depending on the protonation state of the receptor. To our knowledge, this is the first example of both halides and water molecules serving the same structural hydrogen-bonding role in a synthetic self-assembled system.[13]

Our initial venture into the use of aryl ethynyl scaffolds as receptor molecules focused on sulfonamide-bearing 2,6-bis(2-anilinoethynyl)pyridine derivatives **1** and **2** (Scheme 1, py = pyridine), designed to target hydrogen-bonding guest molecules (see the Supporting Information).[14] CAChe semiempirical minimized molecular models suggested that selectivity for different guest molecules could be tailored by protonating the pyridine nitrogen atom, thus altering the cavity size, or by exchanging the binding substituents. The aryl ethynyl core **3** is prepared from 2-iodo-4-*tert*-butylaniline[15] in three steps in 60% overall yield. Conversion to sulfonamides **1** and **2** was accomplished in excellent yield by treatment of **3** with the corresponding sulfonyl chlorides (Scheme 1).



Scheme 1.

Receptor molecules **1** and **2** have been characterized by ^{1}H and ^{13}C NMR, UV/Vis, fluorescence, and IR spectroscopy; melting point; and single crystal X-ray diffraction (see the Supporting Information). Interestingly, the ^{1}H NMR spectroscopy signals of receptors **1** and **2** exhibit considerable concentration dependence in organic solvents. Furthermore, the sharp singlet typically observed at approximately $\delta =$ 1.5 ppm for residual water in $CDCl_3$ appears as a broad downfield singlet (observed as far downfield as 4 ppm, depending on concentration), hinting at the hydrogen-bond-

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ing capability of receptors **1** and **2** in solution. This finding was confirmed by single crystal X-ray diffraction analysis of neutral receptors **1** and **2** (Figure 1).[16,17]

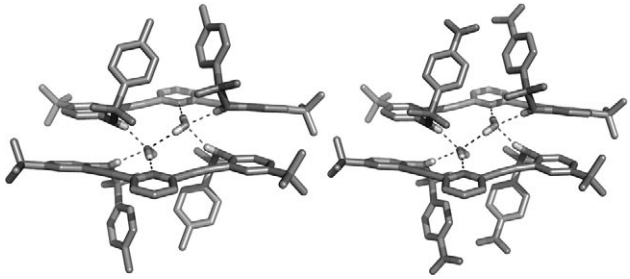

Figure 1. Crystal structures of receptors $(\mathbf{1}\cdot H_2O)_2$ (left) and $(\mathbf{2}\cdot H_2O)_2$ (right) illustrate the 2+2 dimer formed with water. The hydrogen bonds involving water as the donor atom form a helical twist through the center of the binding cavity. All hydrogen bonds are depicted as dashes. For clarity, H atoms not involved in hydrogen bonds were omitted, and only one position for the disordered H atom in the bridging solvent water molecule is shown.

Colorless single crystals of receptors **1** and **2** suitable for X-ray diffraction were grown by layering hexane onto ethyl acetate solutions of each receptor. As suggested from the ^{1}H NMR spectroscopic data, complexes $(\mathbf{1}\cdot H_2O)_2$ and $(\mathbf{2}\cdot H_2O)_2$ both crystallize as dimers in space group $P\bar{1}$ with two receptor molecules and two water molecules per unit cell; consequently, each dimer has crystallographic inversion symmetry. A prominent feature of each crystal structure is the presence of two hydrogen-bonding water molecules stitching the receptor dimers together. The two pyridine nitrogen atoms accept hydrogen bonds from different water molecules (2.797(4)–2.804(2) Å, O–H···N angles 172(4)–175(3)°), while one water–water hydrogen bond is present (2.917(5)–3.006(7) Å, O–H···O angles 164(4)–178(6)°). All of the N-substituted sulfonamides adopt the energetically most favored staggered conformation,[18] and each sulfonamide proton on the receptors donates a hydrogen bond to a different water molecule (2.855(4)–2.860(3) Å, 157(2)–164(3)° and 3.028(4)–3.039(3) Å, 158(2)–164(3)°) such that the 2+2 dimer structure is held together by four sulfonamide–water hydrogen bonds, two pyridine–water hydrogen bonds, one water–water hydrogen bond, and two π-stacking interactions between the receptors ranging from 3.42–3.44 Å (Figure 1).

The dimerization of receptor **1** was further investigated in $CDCl_3$ solution. Receptor **1** was dissolved in water-saturated $CDCl_3$ to a concentration of 197 mM. The sulfonamide N–H and water ^{1}H NMR spectroscopic resonances during a series of dilutions resulted in data that could be fit to a 1:1 dimerization with the nonlinear regression curve fitting software WinEQNMR[19] (see the Supporting Information). In $CDCl_3$, receptor **1** is shown to dimerize with a modest $K_{dim} = 42\ M^{-1}$. Evidence supporting dimerization in $CDCl_3$ solutions resulted from the NOE observed between the protons on the guest water molecules and the sulfonamide protons of the receptor (see the Supporting Information). Receptor **1** exhibits a propensity to crystallize as a dimer with H_2O, even in the presence of other potential neutral guest molecules[20] and in solvents dried over 3-Å molecular sieves.

Receptor molecules **1** and **2** share a common design trait: their ability to alter guest selectivity by simple changes in the protonation state of the receptors. By protonating the pyridine nitrogen atoms of receptors **1** and **2**, the anion-binding capacity of these receptors is activated. The halide-binding properties of $H\mathbf{1}^+$ have been investigated in the solid state. Single crystals of the chloride and bromide complexes are prepared by dissolving receptor **1** or **2** in ethyl acetate and bubbling HCl or HBr gas through the solution. Crystallization is induced by layering hexanes onto the yellow ethyl acetate solutions. Strikingly, the crystal structures of the $H\mathbf{2}^+\cdot Cl^-$ and $H\mathbf{1}^+\cdot Br^-$complexes revealed nearly isostructural dimers to those observed for the neutral $(\mathbf{1}\cdot H_2O)_2$ and $(\mathbf{2}\cdot H_2O)_2$ water dimers.[21,22] In the solid state, the $(H\mathbf{2}^+\cdot Cl^-)_2$ and $(H\mathbf{1}^+\cdot Br^-)_2$ dimers (Figures 2a and 3d, respectively) are held together by four sulfonamide hydrogen bonds (3.156(2)–3.229(2) Å, N–H···Cl angles 151(2)–171(3)°; 3.338(5)–3.440(6) Å, N–H···Br

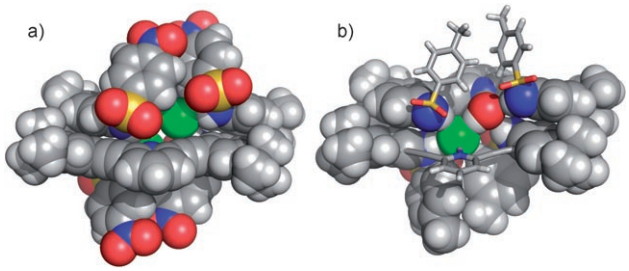

Figure 2. a) Space-filling representation of the crystal structure of $(H\mathbf{2}^+\cdot Cl^-)_2$. b) Crystal structure of the water–chloride heterodimer $(H\mathbf{1}^+\cdot Cl^-)\cdot(\mathbf{1}\cdot H_2O)$. Both water and hydrogen chloride stabilize dimer formation, with seven hydrogen bonds within the binding cavity of the heterodimer. Only one position of the disordered water molecule and chloride ion is shown for clarity. Cl green, S yellow, N blue, O red, C gray, H light gray.

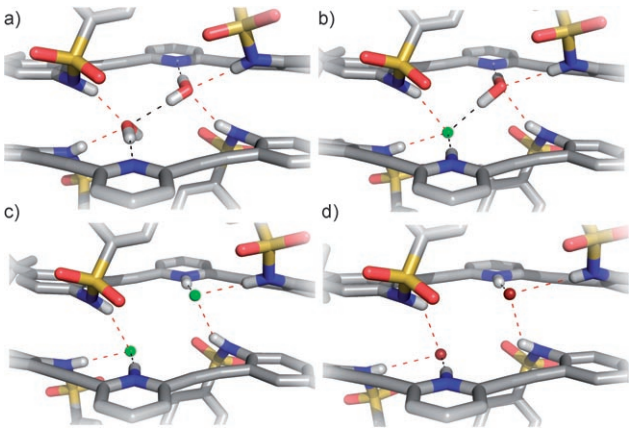

Figure 3. Wireframe representations of the crystal structures of a) $(\mathbf{1}\cdot H_2O)_2$, b) $(H\mathbf{1}^+\cdot Cl^-)\cdot(\mathbf{1}\cdot H_2O)$, c) $(H\mathbf{2}^+\cdot Cl^-)_2$, and c) $(H\mathbf{1}^+\cdot Br^-)_2$ highlighting the interchangeable role that halides and water play in the dimerization of 2,6-bis(2-anilinoethynyl)pyridine sulfonamide receptors. Hydrogen bonds are illustrated as dashes (sulfonamide in red and all others in black). Hydrogen atoms not involved in H-bonds are omitted for clarity. Cl green, Br maroon, S yellow, N blue, O red, C gray, H light gray.

angles 136(4)–168(4)°), two pyridinium N–H hydrogen bonds to the anions (3.022(2) Å, 175(3)° for $(H\mathbf{2}^{+}\cdot Cl^{-})_2$ and 3.127(6) Å, 173(4)° for $(H\mathbf{1}^{+}\cdot Br^{-})_2$), two C_{aryl}–H···X hydrogen bonds (3.69–3.90 Å), and two π-stacking interactions between receptors (3.49 Å for $(H\mathbf{2}^{+}\cdot Cl^{-})_2$ and 3.61 Å for $(H\mathbf{1}^{+}\cdot Br^{-})_2$). The numerous hydrogen bonds and unique dimerization bring the negatively charged halides into close proximity, with halide–halide distances of 3.92 Å for $(H\mathbf{2}^{+}\cdot Cl^{-})_2$ and 4.08 Å for $(H\mathbf{1}^{+}\cdot Br^{-})_2$.

CAChe semiempirical calculations of the 2,6-bis(2-anilinoethynyl)pyridine receptors suggested that larger polyatomic anions would not fit within the binding pocket of the receptor. As predicted, the single crystal X-ray structure of the HBF_4 salt $H\mathbf{1}^{+}\cdot BF_4^{-}$ reveals that the binding pocket is too small to accommodate the interaction of the large BF_4^{-} guest with either sulfonamide proton.[14] Dilution experiments with $H\mathbf{1}^{+}\cdot BF_4^{-}$ revealed minimal change in the ^{1}H NMR spectrum upon addition of $CDCl_3$, thus indicating negligible dimerization in solution as predicted by the receptor conformation observed in the crystal structure.[14] However, titrations of $H\mathbf{1}^{+}\cdot BF_4^{-}$ with tetra-*n*-butylammonium halide salts do indicate that anion binding occurs in solution between the receptor and halides.[23] Furthermore, the concentration dependence observed in the ^{1}H NMR spectrum upon dilution of $(H\mathbf{1}^{+}\cdot Cl^{-})_2$ in $CDCl_3$ indicates the presence of a receptor–halide dimer in solution. A supersaturated solution of $(H\mathbf{1}^{+}\cdot Cl^{-})_2$ (60 mM) was obtained by passing HCl gas through a $CDCl_3$ solution of neutral receptor **1**. Plotting the changes in chemical shift upon dilution and subsequent fitting of this data to a 1:1 dimerization model with the nonlinear least squares regression program WinEQNMR resulted in a $K_{dim} = 250\ M^{-1}$ in $CDCl_3$.[24] Further evidence of dimerization was obtained by mixing receptor **1** and a *p*-methoxyphenyl sulfonamide derivative in a 1:1 ratio.[14] When equimolar mixtures of these receptors are prepared in $CDCl_3$ (10 mM) and HCl gas is passed through the solution, the resulting ^{1}H NMR spectroscopy signals are shifted from the signals observed for either of the analogous homodimers prepared in the same way at the same concentration. This result suggests that both homodimers and a third species, the heterodimer, are present in solution but equilibrate quickly on the NMR timescale. From all of these experiments, it is evident that dimerization of both the neutral and protonated forms of 2,6-bis(2-anilinoethynyl)pyridine receptors occurs and that these dimers persist in the solid state and in solution.

Remarkably, a different type of heterodimer, $(H\mathbf{1}^{+}\cdot Cl^{-})\cdot\mathbf{1}\cdot H_2O$), was also crystallized in the presence of concentrated HCl with one water molecule and one chloride in the binding pocket (Figures 2b and 3b).[25] The heterodimer contains one protonated receptor that binds a chloride anion, while the other receptor in the dimer is neutral and bound to a water molecule. Water and hydrogen chloride are freely exchangeable in this binding pocket and provide structural features that are intermediate to those in the H_2O and hydrogen halide dimers. Analogous to the other dimers presented, the heterodimer is stabilized by π-stacking interactions between the two receptors (3.43 Å) and by a series of seven guest-assisted hydrogen bonds. Each guest water molecule and chloride ion accepts two sulfonamide N–H hydrogen bonds (3.157(3)–3.181(3) Å, N–H···X angles 158(3)–167(3)°) and additionally forms a helical hydrogen-bonding pattern running between the pyridinium nitrogen atom, chloride ion, water molecule, and pyridine nitrogen atom (2.926(3)–3.10 Å, 164(3)–176(4)°). Two C_{aryl}–H···Cl hydrogen bonds (3.76–3.93 Å) also stabilize the dimer.

In conclusion, we have investigated the host–guest chemistry of a new class of hydrogen-bonding receptors. Sulfonamide-substituted 2,6-bis(2-anilinoethynyl)pyridine derivatives exhibit guest-assisted dimerization with H_2O, hydrogen halides, or both, where water and halide anions surprisingly share the same structural role, depending on the protonation state of the receptor. In fact, on the basis of the heterodimer $(H\mathbf{1}^{+}\cdot Cl^{-})\cdot(\mathbf{1}\cdot H_2O)$ (Figure 3), water and hydrogen chloride appear to be completely interchangeable structural partners in facilitating the dimerization. The persistence of guest-assisted dimerization has also been observed in solution. In particular, ^{1}H NMR spectroscopy dilution experiments have been used to observe the dimerization behavior of the neutral sulfonamide with water and the protonated sulfonamide with chloride. Both UV/Vis and ^{1}H NMR spectroscopy have been used to assess the association of $H\mathbf{1}^{+}$ with anions in solution (Cl^-, Br^-, and I^-), and further investigations are underway to quantify the strength of the interactions in solution. We are interested in using our modular approach to synthesize 2,6-bis(2-anilinoethynyl)pyridines designed to target different guest molecules, depending on the binding substituent attached to the receptor. The extended conjugation inherent in 2,6-bis(2-anilinoethynyl)-pyridine derivatives produces distinct emission properties that will be used to monitor interactions with guest molecules.[14] This observation bodes well for the use of 2,6-bis(2-anilinoethynyl)pyridine derivatives as sensors for the selective recognition of guest molecules.

Experimental Section

Full experimental details, including structural details for all compounds described (in cif format), a general X-ray diffraction experimental section (including discussion of disorder modeling), syntheses of all receptors from key intermediate **3**, NOE spectrum of $(\mathbf{1}\cdot H_2O)_2$, details of crystallization and dimerization experiments, video representation of the $(\mathbf{1}\cdot H_2O)_2$ crystal structure, and any associated references are available in the Supporting Information. CCDC-657490, 657491, 957492, 657943, and 657494 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[16] Crystal data for $(\mathbf{1}\cdot H_2O)_2$: $(C_{43}H_{45}N_3O_5S_2)_2$, $M_r = 1495.88$, $0.31 \times 0.18 \times 0.15$ mm, triclinic, space group $P\bar{1}$, $a = 10.0377(17)$, $b = 12.755(2)$, $c = 17.357(3)$ Å, $\alpha = 111.270(3)$, $\beta = 96.113(3)$, $\gamma = 102.966(3)°$, $V = 1974.4(6)$ Å^3, $Z = 1$ (one dimer per unit cell), $\rho_{calcd} = 1.258$ g mL^{-1}, $\mu = 0.183$ mm^{-1}, $2\theta_{max} = 54.00°$, $T = 173(2)$ K, $R1 = 0.0470$ for 6966 reflections (662 parameters) with $I > 2\sigma(I)$, and $R1 = 0.0580$, $wR2 = 0.1222$, and GOF = 1.028 for all 8480 data, max/min residual electron density $+0.502/-0.682$ e Å^{-3}.

[17] Crystal data for $(\mathbf{2}\cdot H_2O)_2$: $(C_{41}H_{39}N_5O_9S_2)_2$, $M_r = 1619.78$, $0.30 \times 0.20 \times 0.01$ mm, triclinic, space group $P\bar{1}$, $a = 10.1068(15)$, $b = 12.5999(19)$, $c = 17.186(3)$ Å, $\alpha = 110.709(3)$, $\beta = 97.006(3)$, $\gamma = 100.306(3)°$, $V = 1972.9(5)$ Å^3, $Z = 1$, $\rho_{calcd} = 1.363$ g mL^{-1}, $\mu = 0.198$ mm^{-1}, $2\theta_{max} = 54.00°$, $T = 173(2)$ K, $R1 = 0.0642$ for 4980 reflections (674 parameters) with $I > 2\sigma(I)$, and $R1 = 0.1233$, $wR2 = 0.1462$, and GOF = 1.034 for all 8413 data, max/min residual electron density $+0.312/-0.432$ e Å^{-3}.

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[21] Crystal data for $(H\mathbf{1}^+\cdot Br^-)_2$: $(C_{43}H_{44}BrN_3O_4S_2)_2$, $M_r = 1621.68$, $0.21 \times 0.07 \times 0.02$ mm, triclinic, space group $P\bar{1}$, $a = 9.632(16)$, $b = 13.33(2)$, $c = 17.47(3)$ Å, $\alpha = 108.39(4)$, $\beta = 94.56(5)$, $\gamma = 106.51(4)°$, $V = 2005(6)$ Å^3, $Z = 1$, $\rho_{calcd} = 1.343$ g mL^{-1}, $\mu = 1.175$ mm^{-1}, $2\theta_{max} = 54.00°$, $T = 173(2)$ K, $R1 = 0.0598$ for 5748 reflections (599 parameters) with $I > 2\sigma(I)$, and $R1 = 0.1021$, $wR2 = 0.1527$, and GOF = 1.035 for all 8622 data, max/min residual electron density $+0.680/-0.371$ e Å^{-3}.

[22] Crystal data for $(H\mathbf{2}^+\cdot Cl^-)_2$: $(C_{41}H_{38}ClN_5O_8S_2)_2$, $M_r = 1656.66$, $0.30 \times 0.25 \times 0.02$ mm, triclinic, space group $P\bar{1}$, $a = 9.8907(13)$, $b = 12.9533(17)$, $c = 17.012(2)$ Å, $\alpha = 107.831(2)$, $\beta = 95.845(2)$, $\gamma = 103.618(2)°$, $V = 1980.5(4)$ Å^3, $Z = 1$, $\rho_{calcd} = 1.389$ g mL^{-1}, $\mu = 0.262$ mm^{-1}, $2\theta_{max} = 54.00°$, $T = 173(2)$ K, $R1 = 0.0572$ for 6572 reflections (594 parameters) with $I > 2\sigma(I)$, and $R1 = 0.0744$, $wR2 = 0.1594$, and GOF = 1.045 for all 8472 data, max/min residual electron density $+0.564/-0.290$ e Å^{-3}.

[23] The UV/Vis spectrum of $H\mathbf{1}^+\cdot BF_4^-$ is consistent with the yellow color of the protonated receptor in organic solutions. Upon protonation, receptor **1** exhibits a new absorption peak with $\lambda_{max} = 400$ nm. The unique absorption characteristics of receptor $H\mathbf{1}^+$ were used to study the host–guest interactions of this molecule in solution. Specifically, tetra-*n*-butylammonium halides were titrated into CH_2Cl_2 solutions of $H\mathbf{1}^+\cdot BF_4^-$ while maintaining constant receptor concentrations. Evident changes in the UV/Vis spectra were observed upon addition of halide anions. In all cases, the absorption bands at 240, 290, and 330 nm were shown to increase in intensity throughout the titration, while the intensity of the absorption band at 400 nm decreased, exemplifying isosbestic behavior. Unfortunately, at low concentrations equilibrium conditions were not observed, precluding the determination of binding constants by UV/Vis spectrophotometric titrations. ^{1}H NMR spectroscopic titrations in $CDCl_3$ were employed to examine the anion-binding capability of receptor $H\mathbf{1}^+$ for tetra-*n*-butylammonium halides. The binding isotherms obtained from titrations of $H\mathbf{1}^+\cdot BF_4^-$ with halides exhibit a steep linear increase up to one equivalent of halide, with chloride affecting the steepest binding isotherm and iodide the shallowest. The second portion of the equilibrium exhibits a much smaller influence on the overall chemical shift of the complex. The second portion of the binding isotherm has made it difficult to determine association constants. Host–guest equilibria will be reported in due course.

[24] Subsequent iterations of this experiment resulted in the formation of precipitate, suggesting that the first trial was supersaturated. The relatively low solubility of this complex in organic solvents has hindered further determination of association constants.

[25] Crystal data for $(H\mathbf{1}^+Cl^-)\cdot(\mathbf{1}\cdot H_2O)$: $(C_{43}H_{43}N_3O_4S_2)_2\cdot H_2O\cdot HCl$, $M_r = 1514.32$, $0.20 \times 0.08 \times 0.02$ mm, triclinic, space group $P\bar{1}$, $a = 9.9702(13)$, $b = 12.8868(17)$, $c = 17.363(2)$ Å, $\alpha = 111.314(2)$, $\beta = 95.475(3)$, $\gamma = 103.737(2)°$, $V = 1977.7(4)$ Å^3, $Z = 1$, $\rho_{calcd} = 1.271$ g mL^{-1}, $\mu = 0.215$ mm^{-1}, $2\theta_{max} = 54.00°$, $T = 173(2)$ K, $R1 = 0.0671$ for 5583 reflections (559 parameters) with $I > 2\sigma(I)$, and $R1 = 0.1074$, $wR2 = 0.1673$, and GOF = 1.027 for all 8485 data, max/min residual electron density $+0.842/-0.723$ e Å^{-3}.

