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A new sulfonamide derivative as magnesium ion receptor: *N*-tosyl-2,6-diisopropyl-4-(2,3-dimethoxylbenzoylamide)aniline

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ABSTRACT

N-Tosyl-2,6-diisopropyl-4-(2,3-dimethoxylbenzoylamide)aniline (**1**) has been synthesized and its metal ion (Na^+, K^+, Ca^{2+}, Mg^{2+}) coordinating properties investigated by FT-IR, ESI-MS, and ^1H NMR methods. Among the tested metal ions, the overall stability constant (log *K*) for Mg^{2+} (6.89) is the highest (Na^+, 5.64; K^+, 5.43; Ca^{2+}, 5.51) in 10% water/THF at 25.0 ± 0.5 °C determined by UV–vis spectroscopy, indicating that **1** is a potent ionophore for Mg^{2+} ion.

Magnesium is the dominant divalent intracellular cation and is essential for a variety of cellular processes such as enzyme function, DNA and protein synthesis, and the regulation of ion channels.[1] Despite the abundance and importance of magnesium, little is known about the molecular nature of proteins involved in cellular magnesium transport at the molecular level.[1,2] The amide group as a peptide linkage unit binds Ca^{2+} in Ca-selective proteins, and is the donor in potassium ion channels and probably also in Ca^{2+} and Na^+ ion channels.[3] At the same time, the amide donors are of considerable importance in the acylamide oxidization or metal cation coupling cases.[4] Sulfonamide derivatives are the most important class of drugs, displaying activities including antibacterial, anticarbonic anhydrase, diuretic, hypoglycemic, and antithyroid effectiveness.[5] In view of these facts, it should be interesting to introduce the amide moiety with metallophilic properties[6] into sulfonamide derivatives[7a,8] to make use of both functionalities in the potentiation of biological activities. Although a few examples (e.g., coumarin 343 and nitrilotriacetamide)[6] showed that amide donor could selectively bind and sense some metal ions, such as Ca^{2+}, Mg^{2+}, Cd^{2+}, Pb^{2+}, Ni^{2+}, and La^{3+};[7,8] in fact, very little attention has been paid to the sulfonamide analogues containing acylamide moiety as an appropriate metal ionophore.

In this Letter, we present the structural and spectroscopic characterization of a new sulfonamide compound **1** and its metal ion affinities. The receptor **1** shows a relatively high selectivity to the magnesium ion over alkali metal ions (Na^+, K^+) and other alkaline earth metal ions (Ca^{2+}).

Compound **1** was synthesized by the reaction of 2,3-dimethoxyl benzoyl chloride with *N*-tosyl-4-amino-2,6-diisopropyl aniline[9] under mild conditions in 78% yield (Scheme 1).[10] Colorless crystals of **1** were obtained from a dichloromethane solution.[11] Structural analysis shows that the central phenyl ring is nearly coplanar with the dimethoxy-substituted phenyl group (dihedral angle: 6.22°). There is an intramolecular N–H···O hydrogen bond between the amide N2H and a methoxy group (O1···N2, 2.674(6) Å; N2–H2A···O1, 141°; Fig. 1). The extended solid-state structure of **1** is derived mainly from intermolecular hydrogen bonding and π–π stacking interactions. A pair of symmetry-related N–H···O hydrogen bonds in the $R_2^2(8)$ motif between the sulfonamide N1H group and one sulfonyl oxygen atom connects two molecules into a dimer, which is further linked by π–π stacking interactions into a one-dimensional chain along the *a*-axis (Fig. S1, see Supplementary data).

In the infrared spectrum of **1** (Fig. 2A (a)), the bands at 3289 and 3250 cm^{-1} are assigned to the N–H stretching vibration, and the strongest band at 1660 cm^{-1} is due to the stretching of the C=O group. The N–H bending vibrations of amide groups are at 1596, 1577, and 1548 cm^{-1}, and the characteristic strong bands at 1267 and 1325–1303 cm^{-1} can be attributed to C–O and O=S=O. To examine its cation sensing properties, compound **1** was mixed with equimolar alkali metal or alkaline earth metal chloride (NaCl, KCl, $CaCl_2$, or $MgCl_2{\cdot}6H_2O$, respectively) in methanol and stirred until complete dissolution, and then dried under vacuum at

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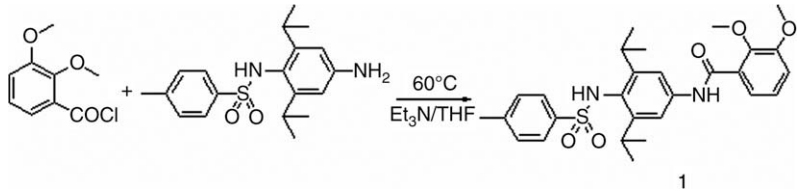


Scheme 1. Synthesis of **1**.

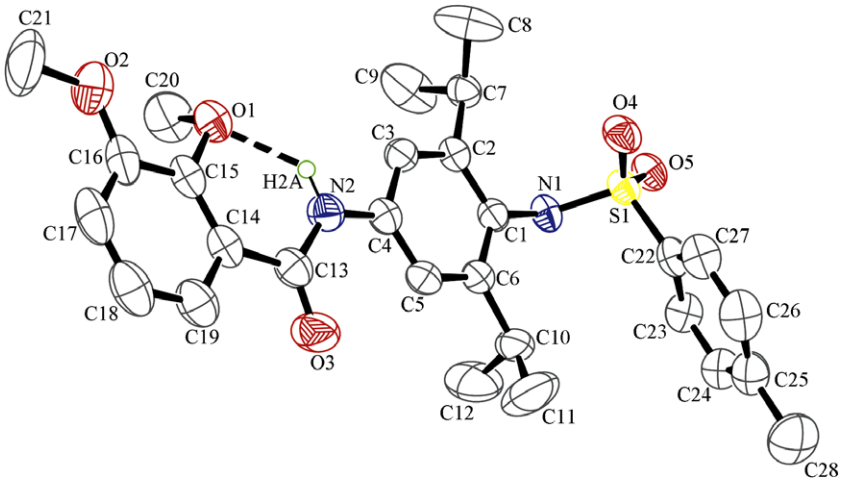


Figure 1. Molecular structure of **1**, showing the intramolecular N–H···O hydrogen bond (thermal ellipsoids at 50% probability level; noninteracting hydrogen atoms are omitted for clarity.). Selected bond distance (Å): N2–C4, 1.409(3); N2–C13, 1.352(3); N1–C1, 1.444(3); S1–O4, 1.420(2); S1–O5, 1.434(2).

50 °C. There was no obvious change in their FT-IR spectra except that of the Mg-loaded adduct, in which the vibration of carbonyl at 1660 cm^{-1} split into two bands (1660, 1631 cm^{-1}; Fig. 2A). When the metal-to-receptor ratio was increased to 5:1, the C=O stretching for the Ca^{2+} and Mg^{2+} adducts completely shifted to 1629 and 1634 cm^{-1}, respectively (Fig. 2B), indicating the transfer of the lone pair electrons from oxygen to metal, which leads to the relaxation and bathochromic shift of the C=O group.

In addition, π-electron delocalization of the aryl ring generated an approximate π–π conjugation cumulative double bonds of C_{aryl}=C=O asymmetric stretching at 2107 and 2247 cm^{-1} for the Ca^{2+}- and Mg^{2+}-treated samples.[12] The wide and strong bands at 472 and 559 cm^{-1} are ascribed to Mg–O and Ca–O bond formation, respectively.[13] In contrast, the alkali metals Na^+ and K^+ showed little influence on the infrared absorption of **1**, suggesting that the binding ability of **1** with Na^+ or K^+ is much weaker than with Ca^{2+} or Mg^{2+}, which is probably due to the far lower charge density of Na^+ (1.05 q $Å^{-1}$) and K^+ (0.75 q $Å^{-1}$) than of Mg^{2+} (2.32 q $Å^{-1}$) and Ca^{2+} (1.75 q $Å^{-1}$).[6b] The electronic delocalization may also affect the N–H stretching, but the broad peak of water at 3200–3500 cm^{-1} caused by deliquescence of the Ca^{2+} or Mg^{2+} adducts most probably shielded the stretching absorbance of N–H. The vibration absorption of O=S=O in all samples remained unchanged. These results indicate the preference of the amide group to metal ions via formation of the M–O=C bond.[8]

Electronic spectral titrations were performed to study the affinity of **1** to different metals. Binding constants for the 1:1 complexation were obtained by a nonlinear least-square fit of the absorbance (X) versus the concentration of the metal ion added (C_M) according to Eq. 1.[14] Stability constants for both 1:1 and 2:1 (L:M) complexes were calculated using the DYNAFIT program.[15] Figure 3a shows the changes in the UV–vis spectrum of **1** upon addition of sodium ion. The band at 277 nm decreased gradually as the concentration of sodium ion increased, and a well-defined isosbestic point was observed at 315 nm. Similar phenomena were also observed in the titration of K^+, Ca^{2+}, or Mg^{2+} to **1**, corresponding to the formation of the 1:1 complex except for the magnesium ion (Fig. S2). The stability constant (log K) of **1** with the three metal ions, Na^+ (5.64), K^+ (5.43), and Ca^{2+} (5.51), is very close (error < 10%, r^2 0.98).

$$X = X_0 + \frac{X_{lim} - X_0}{2C_0} \times \left[C_0 + C_M + 1/K_s - [(C_0 + C_M + 1/K_s)^2 - 4C_0C_M]^{1/2}\right] \quad (1)$$

Mg^{2+} is usually thought to be 'UV-silent' for its stable electron configuration (s^2p^6). However, intense absorption bands occur in the range of 200–350 nm upon addition of **1**. This may be attributed to the charge transfer involving the 'lone pair' on the Mg^{2+}. The variation of these bands with increasing concentration of **1** is seen in Figure 3b. The free Mg^{2+} ion shows a band at about 225 nm, while the highest intensity occurs for 3.7×10^{-3} mol dm^{-3} of **1**. The spectra represent two successive equilibria. The lower intensity set at about 245 nm corresponds to the formation of the mono-ligand complex, while the subsequent set (277 nm) with higher intensity corresponds to the formation of the bis-ligand complex. Therefore the magnesium complexation by **1** should consider both ML and ML_2 stoichiometries. The inset shows that the fit to the curve of the absorbance intensity versus concentration of **1** can be fulfilled by the DYNAFIT program, and the stepwise stability constants for magnesium (log K_1 = 4.50 for ML and log K_2 = 2.39 for ML_2) were calculated. The results show that Mg^{2+} (the smallest cation among the series) has unique chemical properties, and one to two receptor molecules could be accommodated around it.

Mass spectrometry measurements were performed for complexes of **1** with equimolar amounts of K^+, Na^+, Ca^{2+}, and Mg^{2+} (Fig. 4). In the case of the magnesium complex, the stoichiometry

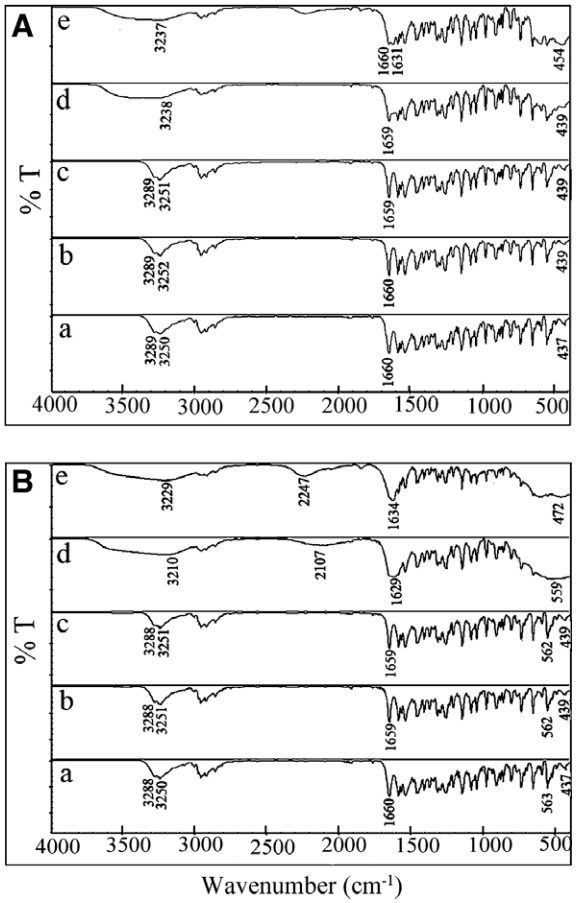


Figure 2. FT-IR spectra of (a) compound **1**, (b) **1** + Na^+, (c) **1** + K^+, (d) **1** + Ca^{2+}, and (e) **1** + Mg^{2+}. The molar ratios of metal-to-receptor are 1:1 (A) and 5:1 (B) in the experiments in (b)–(e).

1:1 is the majority as indicated by signals at *m/z* 267.6 (100.0%, $[L+Mg]^{2+}$) and 569.7 (27.3%, $[L+Mg+Cl]^+$). The minor peak at *m/z* 522.7 (33.0%, $[2L+Mg]^{2+}$) is for the bis-ligand complex. The mass spectra of other metal complexes show only the 1:1 complex. The total content of the magnesium complex is much higher than

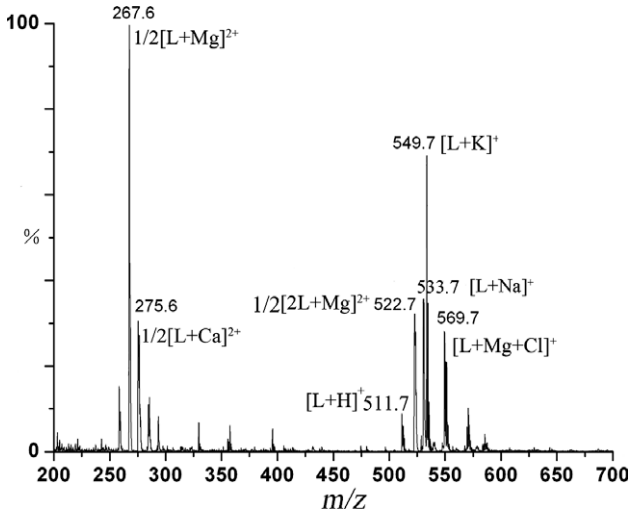


Figure 4. ESI-MS spectrum of **1** with equimolar amounts of sodium, potassium, calcium and magnesium ions in THF solution.

those of other metals ($[L+Na]^+$, *m/z*: 533.7, 39.6%; $[L+K]^+$, *m/z*: 549.7, 64.0%; and $[L+Ca]^{2+}$, *m/z*: 275.6, 29.5%). The results also demonstrate that compound **1** has high selectivity for magnesium ion. Meanwhile, to further validate the abovementioned conclusion, ion chromatographic analyses were performed on this system (Fig. S3, see Supplementary data). According to the relation of ion content corresponding to its peak area, the concentration of Na^+, K^+, Ca^{2+}, and Mg^{2+} extraction in deionized water was calculated as 0.82, 0.50, 0.74, and 0.07 mg dm^{-3}, respectively. The concentration of Mg^{2+} is the lowest, indicating that its complex is the hardest to hydrolyze among these alkali metal or alkaline earth complexes. The results also revealed that the binding ability of **1** to Na^+, K^+, and Ca^{2+} is quite close, as shown by the stability constants.

To clarify the complexation environment of the metal ions with the receptor **1**, ^1H NMR examination was carried out in acetone-d_6 with a 1:1 molar ratio of magnesium chloride hexahydrate and **1**. Changes of the chemical shifts of 'free' ligand **1** and the corresponding complex are shown in Figure 5. Regarding the complexation of **1** with Mg^{2+}, amide proton showed large magnetic shift

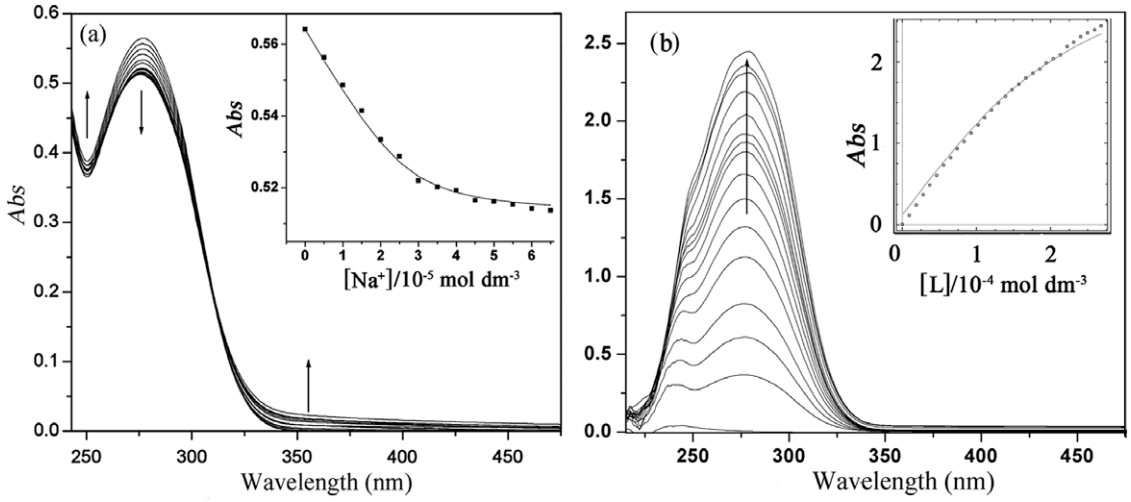


Figure 3. (a) Changes in the absorption spectra of ligand **1** (3.0×10^{-5} mol dm^{-3}) upon titration of sodium chloride in 10% water/THF (1/6 to 5 equiv); (b) absorption spectra of magnesium chloride (1.3×10^{-4} mol dm^{-3}) upon titration of ligand **1** in 10% water/THF (up to 2.1 equiv). Inset: absorbance at 277 nm (■) as a function of [**1**] with theoretical 1:1 and 1:2 (M:L) stoichiometry (–) fits using DYNAFIT program.

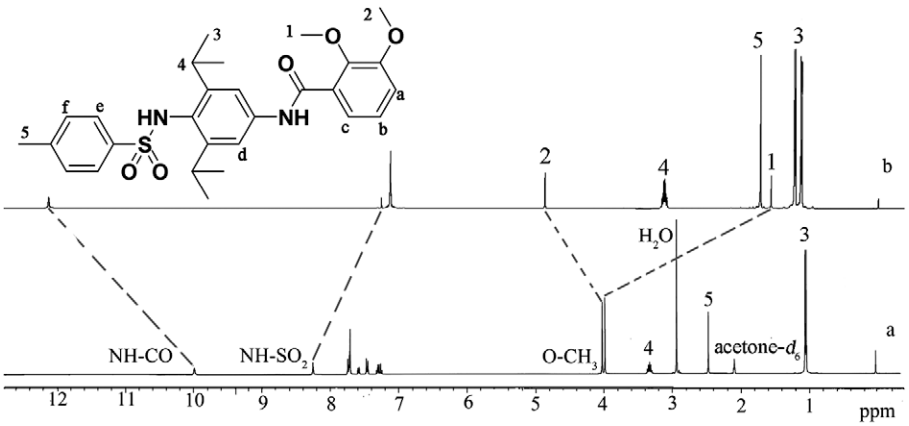
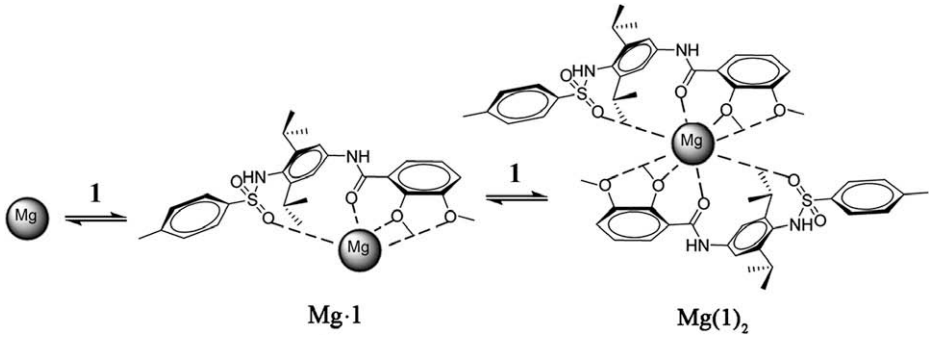


Figure 5. ^{1}H NMR spectra (400 MHz, acetone-d_6) of (a) free 'ligand' **1**, and (b) **1** + $MgCl_2{\cdot}6H_2O$.



Scheme 2. Proposed binding mode for the magnesium complex.

changes ($\Delta\delta$ = +2.21) because of the reduction of electron density on the oxygen atom by coordinated cation. The methoxy proton 2 showed small shift tendency ($\Delta\delta$ = +0.89) due to the weak interaction of the oxygen atom with the metal ion. The aromatic proton signals (a–f) shifted slightly up-field ($\Delta\delta$ = −0.56 to −0.11). In contrast to proton 2, a large up-field shift of proton 1 ($\Delta\delta$ = −2.38) was induced upon complexation. Interestingly, each peak of methyl proton 3 corresponds to a different chemical environment, indicating the formation of a locally distorted structure. Furthermore, sulfonamide NH signals shifted up-field ($\Delta\delta$ = −0.93) upon the addition of metal ions. The result indicates that the contribution of different oxygen-containing groups of the 'ligand' to the complex formation is different. On the basis of FT-IR, UV–vis titration, and ^{1}H NMR studies, plausible structures of the magnesium complexes are illustrated in Scheme 2. We adopt the term coordinative unsaturation to describe the complex Mg·**1** that has more open coordination sites where another ligand could be bonded in a similar fashion.[16]

In summary, we report a new sulfonamide-amide moiety that displays relatively high selectivity to magnesium ion over other alkali metals or alkaline earth metal ions (Na^+, K^+, and Ca^{2+}). FT-IR and ^{1}H NMR spectroscopy showed that the magnesium ion has a strong binding interaction with the carbonyl and the methoxy group adjacent to the carbonyl moiety of **1**. Absorption spectroscopy and ESI-MS spectrometry also revealed the presence of 1:1 and 1:2 stoichiometries (M:L) for the magnesium complexation.

Acknowledgment

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Supplementary data

Crystallographic data for the structure reported in this Letter have been deposited with the Cambridge Crystallographic Data Center (CCDC 713841). Copies of this material can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: ++44 12 23 336 033; email: deposit@ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.005.

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10. *Preparation of N-tosyl-2,6-diisopropyl-4-(2,3-dimethoxyl benzoylamide)aniline*: To a solution of 2,3-dimethoxyl benzoyl chloride (3.8 g, 19 mmol) in THF

(30 mL) was added *N*-tosyl-4-amino-2,6-diisopropyl aniline (6.5 g, 19 mmol) in three portions under stirring. Then NEt_3 (2.6 mL) in dry THF (60 mL) was added dropwise. The mixture was heated to 60 °C for 24 h under N_2. The solvent was removed and the residue was partitioned into a mixture of water (50 mL) and dichloromethane (50 mL). The organic phase was then washed successively with 1 M NaOH (100 mL), 1 M HCl (100 mL) and saline solution (100 mL), and then dried over anhydrous $MgSO_4$. The product was recrystallized from dichloromethane/diethyl ether as a white crystalline material. Yield 7.5 g (78%). Mp: 201–203 °C. Anal. Calcd for $C_{28}H_{34}N_2O_5S$: C, 65.86; H, 6.71; N, 5.49. Found: C, 65.85; H, 6.70; N, 5.35. See Supplementary data for other characterization of **1** (^1H NMR, ^{13}C NMR, IR).

11. *Crystal data for* **1**: $C_{28}H_{34}N_2O_5S$ (510.64), monoclinic, space group *C*2/*c*, $a = 30.371(3)$, $b = 10.981(1)$, $c = 17.667(2)$, $\beta = 111.326(3)°$, $V = 5488.7(10)$ Å^3, $Z = 8$, $D_{calc} = 1.236$ g cm^{-3}, $F(000) = 2176$, $\mu = 0.16$ mm^{-1}, $T = 293(2)$ K, 16507 reflections collected, 6659 independent ($R_{int} = 0.045$), $R_1 = 0.0520$, $wR_2 = 0.1259$ [$I > 2\sigma(I)$].
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