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Unclassical hydrogen bonds of C–H···O and C–H···Cl in the crystals of 1,4-diaryl Hantzsch esters

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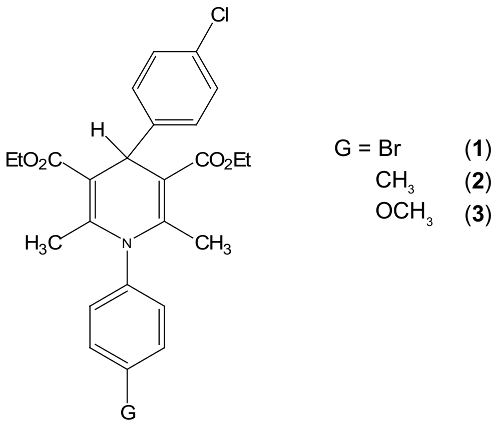
Abstract—Three novel N1-substituted derivatives of Hantzsch ester were synthesized and the molecular structures were studied by using X-ray crystallography. Two types of unclassical hydrogen bonds C–H···O and C–H···Cl were presented in the crystals. The formation of such a hydrogen bond is dependent on the nature of the substituent at C23.

Hantzsch-1,4-dihydropyridine and its derivatives are widely prescribed as calcium β-blocker, and used for the treatment of hypertension and heart defibrillation.[1] Their bio-activity is believed to arise from binding with a receptor site located in the α_1 subunit of the L-type voltage gated channels present in skeletal and cardiac muscle, and is strongly dependent on the molecular conformation and intermolecular force of Hantzsch-1,4-dihydropyridines in their crystals.[2,3] Systematical examination of previous reports on this subject shows that although there are many chemists devoted to the design, syntheses, and crystallographic studies of various derivatives of Hantzsch-1,4-dihydropyridine as candidates of calcium β-blockers,[4] the main attention was limited to the N1-unsubstituted derivatives of Hantzsch-1,4-dihydropyridine. The studies on the crystal structures show that the molecular packing arrangements in crystals are all controlled by N1–H···O hydrogen bond. This raises an interesting question: what are the forces to make the molecules together in the crystals if the hydrogen atom at the N1 position is substituted by aryl or alkyl group? In order to elucidate this interesting question, three N1-substituted Hantzsch-1,4-dihydropyridines: 1-(*p*-bromophenyl)-4-(*p*-chlorophenyl)-Hantzsch-1,4-dihydro-pyridine (**1**), 1-(*p*-methylphenyl)-4-(*p*-chlorophenyl)-Hantzsch-1,4-dihydropyridine (**2**), and 1-(*p*-methoxyl-phenyl)-4-(*p*-chlorophenyls)-Hantzsch-1,4-dihydropyridine (**3**) were designed and synthesized. It is interesting that two types of unclassical intermolecular hydrogen bonds of C–H···O and C–H···Cl are observed for all three compounds, and each molecule is hydrogen bonded with four other molecules. In this letter we wish to report the details (Scheme 1).

Compounds **1**–**3** were synthesized from *p*-chlorobenzaldehyde, ethyl acetoacetate and the appropriate *p*-substituted aniline by condensation.[5] Crystals of the three compounds were obtained by slow evaporation from ethanol solution. The stereoscopic drawings of the molecular packing arrangements seen down from *b*-axis are shown in Figure 1.

The most eye-catching conformational feature of the three compounds is that they all adopt a puckered



Scheme 1.

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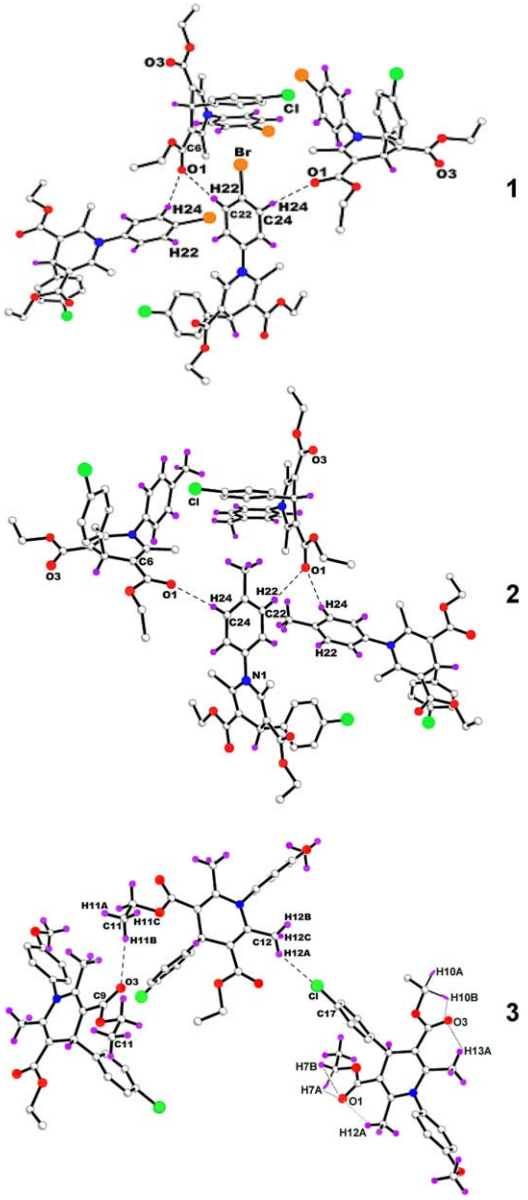

Figure 1. Stereoscopic drawings of the molecular packing arrangement as seen down the *b*-axis for **1**. Also shown are the intermolecular hydrogen bonds. For **1**: C22–H22···O1 (C22–H22 0.923, H22···O1 2.512 Å, C22–H22···O1 159.6) and C24–H24···O1 (C24–H24 0.923, H24···O1 2.536 Å, C24–H24···O1 153.9). For **2**: C22–H22···O1 (C22–H22 0.923, H22···O1 2.511 Å, C22–H22···O1 161.0°) and C24–H24···O1 (C24–H24 0.923, H24···O1 2.538 Å, C24–H24···O1 155.7°). For **3**: C22–H22···O1 (C22–H22 0.923, H22···O1 2.511 Å, C22–H22···O1 161.0°) and C24–H24···O1 (C24–H24 0.923, H24···O1 2.538 Å, C24–H24···O1 155.7°). Some non-interacting hydrogen bonds are omitted for clarity.

boat-like conformation, which is similar to that of some N1-unsubstituted Hantzsch-1,4-dihydropyridines.[6] Since hydrogen atom at the N1 position in **1**–**3** was substituted by aryl group, classical N–H···O hydrogen bond found in the N1-unsubstituted Hantzsch-1,4-dihydropyridines has no condition to exist any longer in the three molecules. In order to discover the new type of intermolecular forces that can link the N1-substituted Hantzsch-1,4-dihydropyridines together in their crystals, distances, and angles of related atoms were examined.

From Figure 1, it is clear to find that for compounds **1** and **2**, the distances from H22 and H24 to O1 in the two vicinal molecules are 2.512 Å (O1···H22), 2.536 Å (O1···H24) for **1**, and 2.511 Å (O1···H22), 2.538 Å (O1···H24) for **2**, respectively, which indicates that the distances from O1 to H22 and from O1 to H24 all are within the distance criteria for a general C–H···O hydrogen bond (2.00–2.80 Å).[7] The angles of O1···H22–C22 and O1···H24–C24 are 159.6°, 153.9° for **1** and 161.0°, 155.7° for **2**, respectively, which are also well in line with the angle criteria for a general C–H···O hydrogen bond (110–180°).[7] These results suggest that H22 and H24 in the same molecule can form two intermolecular hydrogen bonds with two O1 atoms located in the two vicinal molecules, respectively. On the other hand, one O1 atom in **1** and **2** can form two bifurcate intermolecular hydrogen bonds with two hydrogen atoms, one is H22 and the other is H24, but the two hydrogen atoms are not in the same molecule, which indicates that one molecule in the crystals of **1** or **2** can be connected with four neighboring molecules by four intermolecular C–H···O hydrogen bonds. Although one C–H···O intermolecular hydrogen bond in general is relatively weak (about 2 kcal/mol from computer),[8] the sum of the energy for the four C–H···O intermolecular hydrogen bonds is larger than enough the energy of O–H···O, 3–7 kcal/mol to fix the crystals of **1** or **2**. A full examination of Figure 1 shows: (i) in **1** and **2**, only O1 atom can form intermolecular hydrogen bond, while the other oxygen atom (O3) cannot; (ii) only H22 and H24 can form intermolecular hydrogen bond with O1 in an adjacent molecule, while H16 and H18 on the C3-phenyl ring cannot. For the first case, the reason could be that O1 adopts the same direction to the vicinal double bond on the pyridine ring, but O3 takes the opposite direction. The result is that O3 is close to the phenyl ring at C3, of course, and subject to electric and steric shielding effect from the phenyl ring during the formation of a intermolecular hydrogen bond. Similarly, for the second case, the main reason could be the repulsion of two large substituents (carbonyl) locating at the *ortho*-positions of the phenyl group at C3 to prevent the approach of O1 in an adjacent molecule to form hydrogen bond with H16 and H18. Meanwhile at the *ortho*-positions of N1 there are only two small substituents (methyl), which may allow the approach of O1 in an adjacent molecule to form hydrogen bond with H22 or H24.

Being different from the structures of **1** and **2**, in the compound **3** there are two different types of intermolecular hydrogen bonds to be found: O3···H11B–C11 and Cl···H12A–C12 according to the distance measurement (2.567 Å for O3···H11B, 2.790 Å for Cl···H12A) and the related bond angles (169.8° for O3···H11B–C11, 127.8° for Cl···H12A–C12), but no intermolecular hydrogen bonds of O1···H22–C22 and O1···H24–C24 were formed. Examining the structure of **3** shows that, although both carbonyl groups adopt the same direction to the vicinal double bond on the pyridine ring, the environments of O1 and O3 are still different from each other. Paying attention to O1 in **3**, we found that the distances from O1 to H7A, H7B, and to H12A are 2.304, 2.592, and 2.047 Å, respectively. Since the three distances all are within the distance scale of a general C–H···O hydrogen bond,[7] they should be considered as three intra-molecular hydrogen bonds. But for O3 in **3**, only two intra-molecular hydrogen bonds O3···H13A (2.149 Å) and O3···H10B (2.471 Å) were formed, which suggests that O3 still has remaining space to form an intermolecular hydrogen bond with an adjacent molecule. H22 and H24 in **3** cannot form intermolecular hydrogen bonds. The main reason could be that methoxyl at the *ortho*-positions of H22 and H24 is a very strong electron-donating group ($\sigma = -0.27$),[9] stronger than methyl ($\sigma = -0.17$),[9] and much stronger bromine ($\sigma = 0.20$),[9] which makes the negative charge of H22 and H24 to increase, so as to result in disadvantage of H22 and H24 to form hydrogen bond. This result clearly indicates that the type of inter-molecular hydrogen bonds in the three compounds is close dependent on the nature of the substituent at C23. When the substituent is an electron-withdrawing group or a weak electron-donating group, the hydrogen bonds of O1···H22–C22 and O1···H24–C24 were observed, but when the substituent is a strong electron-donating group, the hydrogen bonds of O3···H11B–C11 and Cl···H12A–C12 were observed.

In summary, three novel N1-substituted Hantzsch esters **1**–**3** were synthesized and two types of unclassical hydrogen bonds C–H···O and C–H···Cl were found according to crystallographic data. The formation of the hydrogen bond is dependent on the nature of the substituent at C23. According to the measurement of O3···H11B–C11 and Cl···H12A–C12 in **3**, it can be concluded that the hydrogen atom at sp^3 carbon (methyl in **3**) is able to form hydrogen bond like the hydrogen atom at sp or sp^2 carbon,[10] which is quite rare in the past literatures. Meanwhile, according to the hydrogen bond of Cl···H12A–C12, another interesting conclusion can be made that chlorine also is able to form hydrogen bond like O and N, which, to our best knowledge, appears to be the first observation in the crystals of Hantzsch ester derivatives as calcium β-blocker.

Supplementary data

NMR MS characterization data and the crystallographic data of compounds **1**–**3** are included. The supplementary data is available online with the paper on ScienceDirect.

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