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Five- and six-membered N–H···S hydrogen bonding in aromatic amides

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ABSTRACT

The capacity of sulfur to form intramolecular five- or six-membered S···H–N hydrogen bonding in aromatic amides is assessed. The five-membered S···H–N hydrogen bonding is observed in crystal structures of five compounds, whereas the six-membered S···H–N hydrogen bonding is revealed in crystal structures of three compounds. The trityl group has been used to promote formation of the weak hydrogen bonding because it efficiently inhibits the competition of the intermolecular C=O···H–N hydrogen bonding. (2D) ^{1}H NMR experiments indicate that both patterns also exist in chloroform.

Hydrogen bonding is one of the most versatile noncovalent forces in supramolecular chemistry and crystal engineering.[1] Therefore, in the past decades assessment of discrete hydrogen bonding patterns had received great attention.[2] Strong hydrogen bondings, such as O–H···O, O–H···N, N–H···O, and N–H···N interactions (energy 5–15 kcal/mol), had already been extensively investigated.[3,4] More recently, weaker hydrogen bonds (≤5 kcal/mol), including the C–H···O, C–H···N, and C–H···π interactions, have also been established and found increasing applications in studies of crystal engineering and molecular recognition.[5]

Peptides and proteins contain important sulfur-containing segments, including cysteine and methionine. Hydrogen bonding with sulfur as acceptor is also important in modulating the high-grade structures and functions of many proteins.[6] Therefore, a deep insight of the S···H hydrogen bonding may be of help to understanding protein folding and biomolecular interactions and developing new supramolecular synthons. In the past decade, several intermolecular S···H–N hydrogen bonding patterns had been reported.[7] However, although intramolecular five-membered S···H–N hydrogen bonding has been proposed to exist in aqueous media in aromatic amides,[8] this pattern has been observed only in the crystal structures of several structurally confined molecules.[9] In contrast, crystal structures of simple molecules of this family exhibit only intermolecular C=O···H–N hydrogen bonding.[10] As for the six-membered S···H–N hydrogen bonding pattern, to the best of our knowledge, no X-ray study has been reported to support its existence in aromatic amides. We herein report a X-ray crystallographic and ^{1}H NMR study on these two hydrogen bonding patterns in 2-(methylthio)benzamide and *N*-(2-(methylthio) phenyl)- acetamide derivatives.

Aromatic amides have a great tendency of forming intermolecular C=O···H–N hydrogen bonding. We chose to inhibit this interaction by introducing a large group or other additional interactions.[11] Compounds **1**–**10** were therefore prepared and their X-ray crystal structures obtained.[12] The crystal structures of **1** and **2** are presented in Figure 1. Both compounds exhibit the five-membered S···H–N hydrogen bonding. The S···H(N) distances (r) are 2.48 and 2.78 Å, respectively, which are notably shorter than the sum of the van der Waals radii (3.00 Å), while their torsion angles (θ) are 7° and 54°,[13] respectively. These results show that the

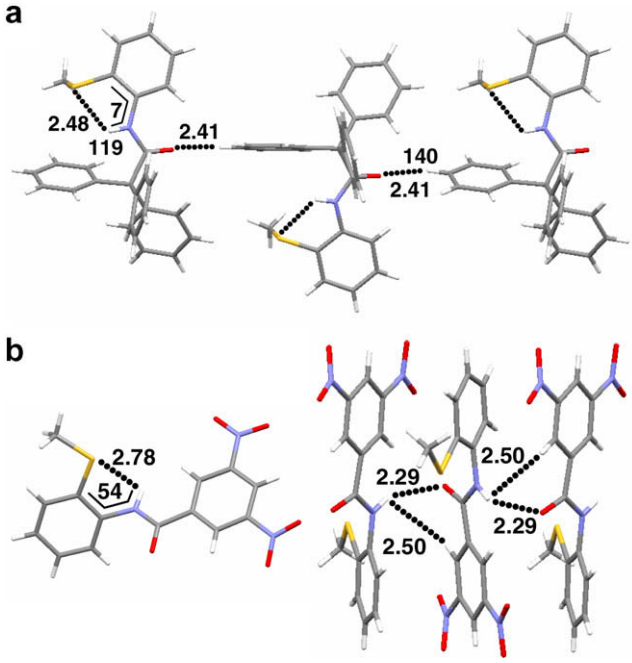

Figure 1. Crystal structures and related bond distance and angle data of (a) **1** and (b) **2**.

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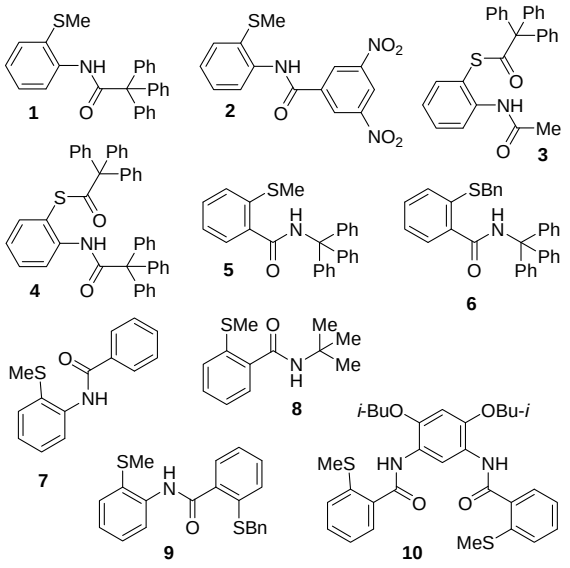
hydrogen bonding in **1** is stronger than that in **2**. This may be ascribed to the trityl unit of **1**, which inhibits the intermolecular C=O···H–N hydrogen bonding. Compound **1** also displays a strong intermolecular C=O···H–C(Ar) interaction (r = 2.41 Å) which stabilizes its packing structure. In contrast, **2** exhibits three-center C=O···H–N (r = 2.29 Å) and C=O···H–C(Ar) (r = 2.50 Å) contacts. These interactions should enhance each other and cause the N–H bond to remarkably deviate from the attached benzene ring, thus weakening its S···H–N hydrogen bonding.



Compound **3** has a more complicated packing pattern. One cell has eight molecules of four conformers (Fig. 2). Two of them exhibit the intramolecular five-membered S···H–N hydrogen bonding (r = 2.84 and 2.80 Å) (Fig. 2b and c). The θ angles (106–108°) of the S–C(=O) bonds of all the conformers deviating from the attached benzene rings are very close. In contrast, the θ values (35°) of the two N–H bonds that are intramolecularly hydrogen bonded are remarkably smaller than those of the other two (103° and 91°). Because the trityl group is located far away from the amide unit, the amide unit is also engaged in four different intermolecular C=O···H–N hydrogen bonds (r = 2.05, 2.14, 2.05, and 2.06 Å), which, together with weak intermolecular C=O···H–C(Ar) and π···H–C(Ar) interactions, control the molecules to pack alternately (not shown).

The crystal structure of **4** also displays intramolecuar five-membered S···H–N hydrogen bonding (r = 2.88 Å) (Fig. 3). Although **4** has two large trityl groups and its sulfur atom has increased effective electronegativity, the hydrogen bonding is considerably weaker than that of **1**. The result implies that, in the absence of competing intermolecular interactions, factors such as the steric effect and molecular shape may also play roles in balancing intramolecular interactions. Interestingly, the (S)C=O oxygen atom is also hydrogen bonded to the amide hydrogen (r = 2.47 Å), leading to an unique intramolecular three-center hydrogen bonding pattern. The two interactions should stabilize each other. As expected, the amide does not form intermolecular hydrogen bonding, but its oxygen atom is engaged in an intermolecular C=O···H–C(Ar) contact.

The crystal structure of **5** reveals an intramolecular six-membered S···H–N hydrogen bond (r = 2.74 Å) (Fig. 4a). The large trityl group makes it impossible for the amide to form intermolecular

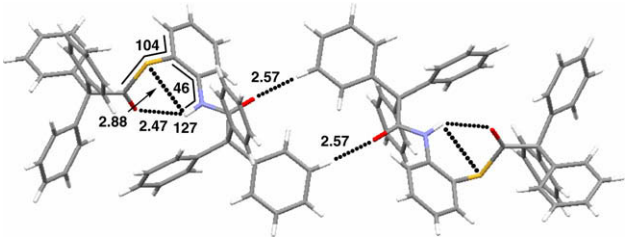


Figure 3. The packing pattern and related bond distance and angle data of **4**.

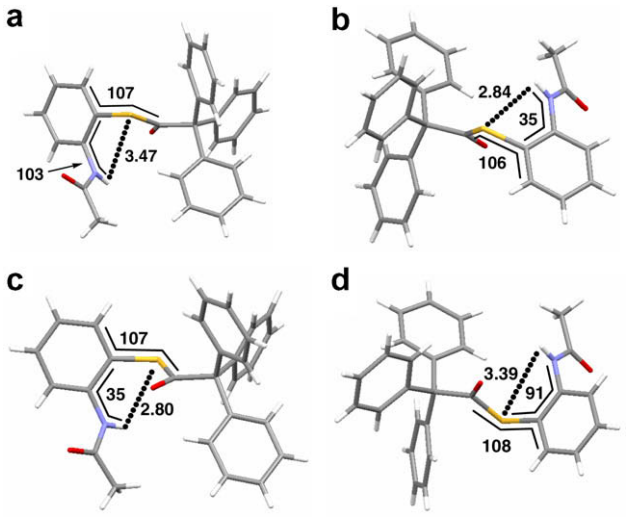


Figure 2. Four conformers of **3** and the related bond distance and angle data.

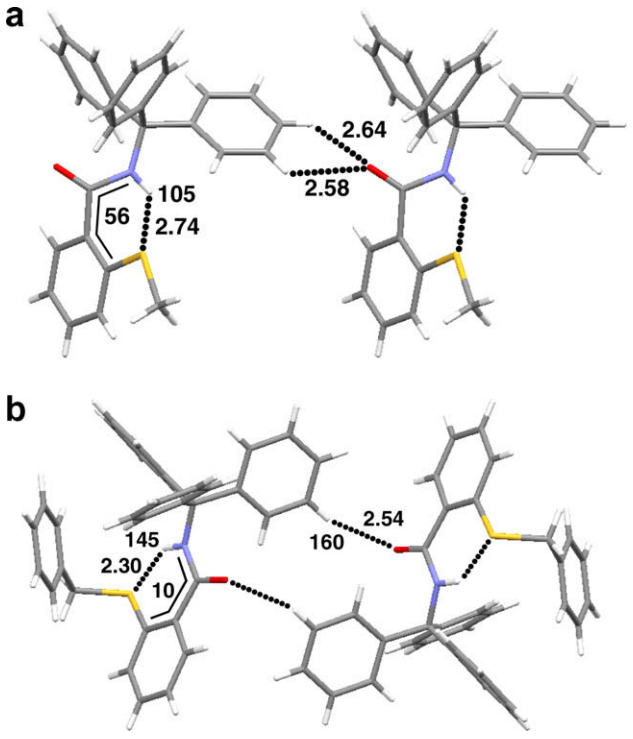


Figure 4. Crystal structures and related bond distance and angle data of (a) **5** and (b) **6**.

C═O···H–N hydrogen bonding. The carbonyl oxygen is therefore engaged in two intermolecular C═O···H–C(Ar) interactions (r = 2.58 and 2.64 Å). Although no intermolecular C═O···H–N interaction is formed, the N–H bond still displays a large torsion (θ = 56°). Compound **6** also forms similar S···H–N hydrogen bonding (r = 2.30 Å, θ = 10°) (Fig. 4b), which is, however, notably stronger than that of **5** due to a reduced torsion angle. Different from that of **5**, the C═O oxygen of **6** forms two intermolecular O···H–C(Ar) interactions with two benzene units and its benzyl ring also has a π···H–C(Ar) contact (not shown) but does not involve π stacking. Clearly, the enhanced S···H–N hydrogen bonding of **6** relative to **5** should be the result of a balance of discrete noncovalent interactions.

The crystal structure of **7** displays a C═O···H–N hydrogen bonding chain (r = 2.06 Å, Fig. 5a), which causes a large torsion (θ = 70°) of the N–H bond from the attached benzene ring and thus a large S···H(N) separation (3.61 Å). The two benzene units do not form intermolecular π stacking, which is in sharp contrast with the result of **2**. The result clearly reveals the importance of a large group in facilitating the formation of the weak S···H–N hydrogen bonding. Compound **8** exhibits a similar C═O···H–N hydrogen bonding chain (Fig. 5b). The hydrogen bonding (r = 2.28 Å) is, however, slightly weaker than that of **7**, as reflected by its larger torsion angle (θ = 42°). A comparison of the result of **8** with that of **5** also shows the importance of a large group for promoting the formation of the S···H–N hydrogen bonding, albeit more results are needed to determine the critical size of the steric group. The crystal structure of **9** (Fig. 5c) exhibits a five-membered S···H–N hydrogen bonding (r = 2.57 Å) that is stronger than that of **2**. This compound was originally designed for exploiting the possible three-center hydrogen bonding pattern, which is common in similar frameworks of oxygen acceptors.[6–8] However, **9** does not give rise to the six-membered S···H–N hydrogen bonding. Instead, its benzylthiol group is orientated to the side of the carbonyl oxygen, leading to intramolecular S···O═C (r = 2.94 Å) and intermolecular C═O···H–C(Ar) (r = 2.57 Å) contacts. The benzyl ring also stacks intermolecularly. Different from **2** or **7**, **9** does not form intermolecular C═O···H–N hydrogen bonding. The result appears to suggest that the five-membered S···H–N hydrogen bonding is more stable than its six-membered one, while the formation of the first hydrogen bonding would be expected to further weaken the capacity of the amide hydrogen to bind to the second sulfur atom.

Compound **10** also exhibits complicated intramolecular interaction patterns because it gives rise to two different conformers (Fig. 6). Conformer A displays no inter-molecular C═O···H–N hydrogen bonding. As expected, its two *i*-butoxyl oxygen atoms are involved in five-membered O···H–N hydrogen bonding. However, only one sulfur atom forms intramolecular six-membered S···H–N hydrogen bonding (r = 2.49 Å), and another one is engaged in strong intramolecular S···O═C interaction (r = 2.66 Å). Conformer B does not exhibit any S···H–N hydrogen bonding. In addition, only one of the *i*-butoxyl oxygen atoms is engaged in intramolecular O···H–N hydrogen bonding. Another one fails because the neighboring amide is heavily twisted from the central benzene ring (θ = 88°). Conformer B also forms two intermolecular C═O···H–N hydrogen bonds (r = 2.29 and 2.51 Å), which not only control the molecular stacking (not shown) but also are the major forces to cause the above large torsion of one of the two amide units.

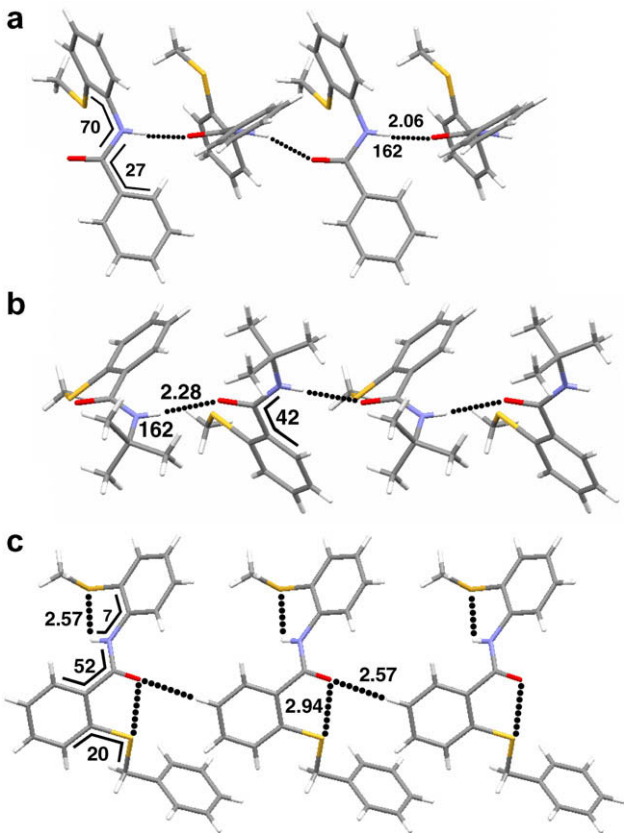


Figure 5. Packing patterns and related bond distance and angle data of (a) **7**, (b) **8**, and (c) **9**.

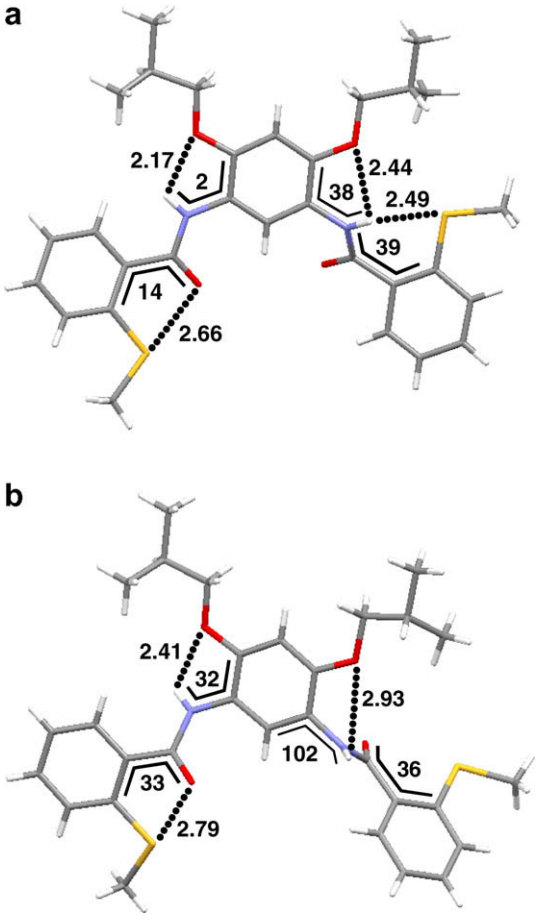
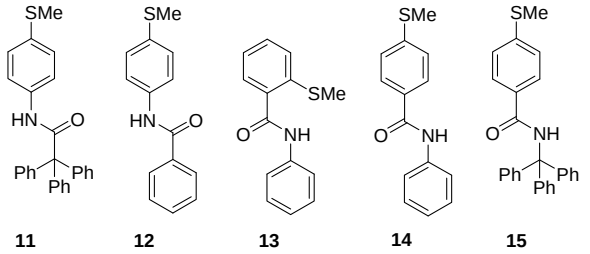


Figure 6. Conformers A (a) and B (b) and related bond distance and angle data of **10**.



To investigate the stability of the intramolecular S···H–N hydrogen bonding in solution, compounds **11**–**15** were also prepared. A comparison of the ^{1}H NMR spectra of the four pairs of isomers **1**/**11**, **7**/**12**, **13**/**14**, and **5**/**15** in $CDCl_3$ and DMSO-d_6 revealed the relative stability of the two hydrogen bonding patterns in solution. Compared to that of their respective isomers **11**, **12**, **14**, and **15**, the chemical shift of the amide hydrogen of **1**, **7**, **13**, and **5** in $CDCl_3$ was all remarkably shifted downfield (Fig. 7), indicating that their amide hydrogen was engaged in intramolecular S···H–N hydrogen bonding. NOESY experiment of **1** in $CDCl_3$ (5.0 mM) also revealed NOE connection between its amide hydrogen and methyl hydrogen but not the 6-H of the thiol-substituted benzene, further supporting the formation of the hydrogen bonding in solution. The differences between the chemical shifts of the amide hydrogen atoms of **1** and **11** ($\Delta\delta$ = 0.80 ppm) and **7** and **12** ($\Delta\delta$ = 1.51 ppm) are notably larger than those between **13** and **14** ($\Delta\delta$ = 0.56 ppm) and **5** and **15** ($\Delta\delta \geqslant 0.34$ ppm),[14] also indicating that the five-membered N–H···S hydrogen bonding is also stronger than the six-membered one in solution. The fact that the crystal structure of **7** does not exhibit intramolecular N–H···S hydrogen bonding may be rationalized by considering that in the solid state molecular packing shortens the distance of the amide units of neighboring molecules and therefore facilitates intermolecular N–H···O=C hydrogen bonding. In solution, however, this intermolecular interaction is concentration-dependent. As a result, at the investigated concentration, it is not strong enough to win the competition with the intramolecular N–H···S hydrogen bonding.

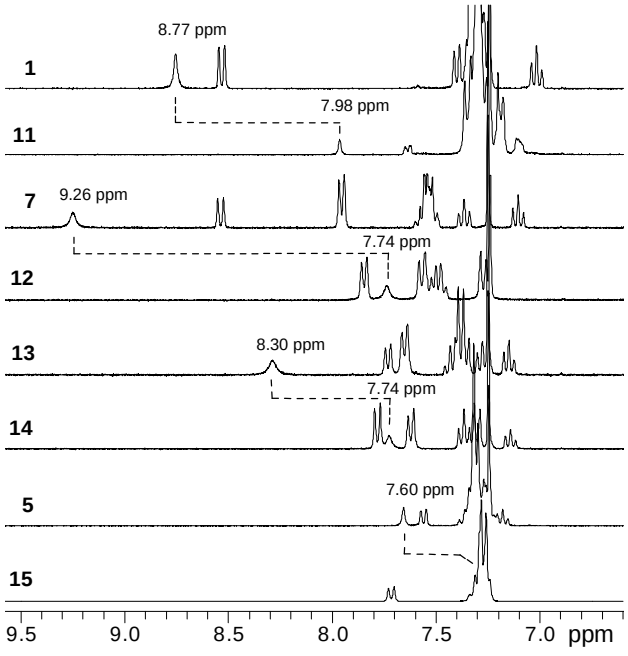


Figure 7. Partial ^{1}H NMR spectra of **1**, **11**, **7**, **12**, **13**, **14**, **5**, and **15** in $CDCl_3$ (5 mM). The signal of the amide hydrogen of **15** was overlapped with others in the upfield area.

^{1}H NMR spectra of **1**, **11**, **5**, and **15** in DMSO-d_6 were also recorded (5 mM). Their NH signals appeared at 8.69, 9.06, 9.01, and 8.89 ppm, respectively. It can be found that the value of **1** is very close to that recorded in $CDCl_3$ ($\Delta\delta$ = −0.07 ppm), implying that its intramolecular N–H···S hydrogen bonding is rather strong and survives even in the highly polar solvent. In contrast, very large shifting was exhibited for the NH signal of **11**, **5**, and **15** ($\Delta\delta \geqslant 1.66$, 1.33 and 1.59 ppm, respectively) when the solvent was changed from $CDCl_3$ to DMSO-d_6. The value of **5** is notably smaller than that of **15**, further suggesting that the amide hydrogen of **5** forms weak six-membered N–H···S hydrogen bonding in chloroform.

In conclusion, this Letter provides the first systematic study on the stability of intramolecular five- and six-membered N–H···S hydrogen bonding in aromatic amides in both the solid and solution phases. We demonstrate that introduction of a trityl unit can efficiently weaken the competition of the stronger intermolecular N–H···O=C hydrogen bonding through steric hindrance and therefore promote the formation of the weak intramolecular bonding. In contrast, the approach of inhibiting the intermolecular N–H···O=C hydrogen bonding by introducing additional strong intramolecular N–H···O hydrogen bonding does not work well, possibly due to that it simultaneously reduces the capacity of the amide protons to bind to sulfur atom. The crystal structures described herein also show a diversity of the intra- and intermolecular interactions. Clearly, it is a balance of numerous discrete interactions including hydrogen bonding, halogen bonding, S···O, C–H···π, and π–π stacking interactions that controls the formation of the final molecular structures. An unexpected observation of this study is that the amide proton of **4** simultaneously binds to the thioester sulfur and oxygen atoms, giving rise to an interesting three-center hydrogen bonding pattern. We are currently investigating the stability and scope of this new pattern.

Acknowledgments

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12. Crystallographic data for **1**–**10** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC 706472–706481. These data can be obtained free of charge via the internet www.ccdc.cam.ac.uk/conts/retrieving.html or by sending an email to deposit@ccdc.cam.ac.uk.
13. This θ value is defined by the torsion angle of the N–H or C=O bond from the attached benzene ring.
14. Since the NH signal of **15** in $CDCl_3$ was overlapped with other signals, its chemical shift was taken as that of the downfield borderline of the overlapping area.