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# DENSITY FUNCTIONAL THEORY STUDY OF EQUIMOLAR COMPLEXATION OF UREA OR THIOUREA WITH 2-ALCOXYBENZAMIDE

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The equimolar complexation behavior of urea or thiourea with 2-alcoxybenzamides has been studied by theoretical calculations. Structural models for the calculation were constructed from the X-ray crystallographic structures of 2-methoxybenzamide (MB) crystal and 2-ethoxybenzamide (EB)-thiourea, MB–thiourea, and MB–urea equimolar cocrystals. Structural optimization for EB—urea equimolar cocrystal was performed by the density functional theory (DFT) method (B3LYP/6-31G** level) and the complexation energy was determined using the DFT with higher order basis set (6-31+G**). Energetic stabilization by the equimolar complexation was observed in the three equimolar complexes. The reason why the amide group of MB is out-of-plane in unprocessed MB crystals is well explained by the calculations. It was suggested that intermolecular hydrogen bonding increases in the out-of-plane structure of MB and that subsequently leads to stabilization in the crystal. The amide group of MB or EB was in-plane by the complex formation with urea or thiourea. Finally, we predict the possibility of EB–urea equimolar complex formation in terms of the complexation energy.

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**Keywords:** density functional theory, equimolar complex, complexation energy, hydrogen bond; urea, thiourea.

## INTRODUCTION

Urea and thiourea have been known to form tunnel-type inclusion complexes with various kinds of guest molecules [1, 2]. Differences in the internal diameter of the hexagonal channel determine the guest molecules which can be included. Conventional urea inclusion complexes, which have a smaller internal diameter of 5.5–5.8 Å [2, 3], pack organic molecules such as *n*-alkanes [4], fatty acids [5], and polymers [6] through van der Waals forces. In the case of thiourea, which forms inclusion complexes with an internal diameter of 5.8–7.1 Å, guest molecules such as branched alkanes, alicyclic and aromatic compounds are found [7, 8]. The host-guest stoichiometry is usually 3:1 or more, depending on the size, shape and degree of saturation of the guest molecules [3]. In addition to the tunnel-type inclusion complexes, other types of inclusion complexes or cocrystals have been reported. Thiourea forms a layered-type inclusion complex with a host-guest stoichiometry of 2:1

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with hexamethylenetetramine [9] or 1,2-diazabicyclo[2.2.2]octane [10]. Basicity and the symmetrical location of amines in guest molecules can be an important factor in determining the structural configuration. α,ξ-dinitriles [11] or di- and tricarboxylic acids [12] form specific cocrystals with urea molecules.

Grinding-induced equimolar complex formation of urea or thiourea with 2-alcoxybenzamides, such as ethenzamide (2-ethoxybenzamide; EB) and 2-methoxybenzamide (MB), has also been reported and the crystal structures have been characterized by single-X-ray diffraction measurements [13, 14]. The structures determined were apparently different from those of the tunnel-type inclusion complexes. The structural requirements for the guest molecule to form an equimolar complex have been evaluated using benzamide derivatives. The 2-alcoxybenzamide structure was found to be important for the formation of equimolar thiourea complexes. In the case of MB, specific conformational changes from a distorted to a flattened structure occurred on complexation. The steric effects of the amide and methoxy groups, hydrogen-bond donating and accepting capabilities, and crystal packing requirement could be responsible for the twisting configuration of the MB molecules. However, it is not clear how they would affect equimolar complex formation.

From the complexation experiments it was found that thiourea forms equimolar complexes with EB or MB. Urea also forms a complex with MB but not with EB (Fig. 1) [14]. Intermolecular hydrogen bond formation between thiourea and EB or MB could play an important role for the complex formation. In the case of urea and MB, both an intermolecular hydrogen bond between urea and MB and a hydrogen bond network between urea molecules may be required for equimolar complex formation. The bulkier ethoxy group could hamper the formation of an intermolecular hydrogen bond network between urea molecules and between urea and ethenzamide. However, the structural restraints and the stability difference are not clear from the previous experiments. In this study, we aimed to clarify the mechanism of the equimolar complex formation through theoretical calculations. The structural models for the calculation were constructed based on X-ray crystallographic structures of MB crystals and EB–thiourea, MB–thiourea and MB–urea equimolar cocrystals [13, 14]. For EB–urea equimolar cocrystal, structural optimization was performed by the density functional theory (DFT) method. The energy of the complexation was determined using DFT. Interaction energy by equimolar complexation and the effect of the dihedral angle of MB between C–O and C–N bonds on the intact and the complex structure was evaluated by the calculations.

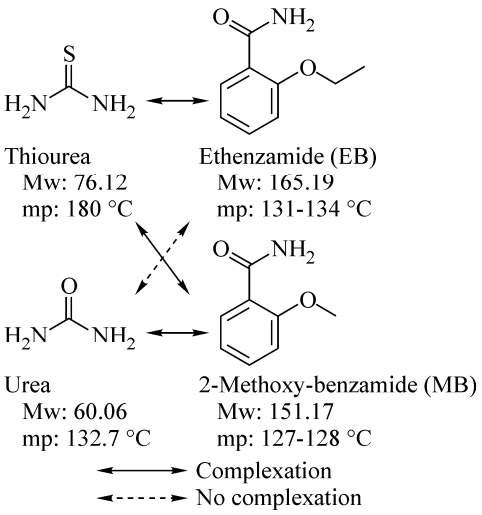


**Fig. 1.** Chemical structures of urea, thiourea, MB, and EB and the behavior.

## EXPERIMENTAL

Based on X-ray crystallographic structure data, we performed calculations of the relative stabilities of the complexes with respect to their components. The crystallographic data of MB, MB–urea and MB–thiourea have been deposited at the Cambridge Crystallographic Data Center in CIF format, CCDC No.262857, 262858 and 262859, respectively. These data can be obtained free of charge from http://www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44-1223-336033.

Calculations were performed at the DFT level using the Gaussian 09 software package [ 15 ]. The hybrid functional B3LYP (Becke′s Three Parameter Hybrid Functional Using the LYP Correlation Functional) was selected for the calculation [ 16, 17 ]. The 6-31+G** basis set was used. Complexation energies ($E_{com}$) were calculated by the following equation:

$$E_{com} = E_{ab} - E_a - E_b,$$

where $E_{ab}$, $E_a$, and $E_b$ are potential energies for complex, MB (or EB) and urea (or thiourea). The total energy of complex was corrected by excluding the basis set superposition error (BSSE) calculated by the Counterpoise corrections [18, 19]. The structure of the EB–urea complex has not been determined yet, because single crystals were not available. However, the complex was reconstructed starting from the MB–urea complex and was optimized at the DFT level. The basis set used was 6-31G**. The calculations in this study were based on the assumption that the intermolecular interactions originated from the two kinds of molecules were limited in a small region of the crystal as reported elsewhere [20, 21]. For this reason, the calculation was conducted using the molecular complex model without adopting periodic boundary condition (PBC) [22].

## RESULT AND DISCUSSION

**Effect of rotation of the amide group of MB on the structural stabilization of unprocessed MB crystals.** The structures of urea, thiourea, MB and EB, and the complexation behavior are shown in Fig. 1. In order to check the position of the amino group of MB, we have defined the torsion angle between alkoxy C–O and amide C–N (O–C1–C2–N, Fig. 2*a*) bonds. The torsion angles were 30.40° in MB intact crystals and 4.46° in both MB–urea and MB–thiourea complexes. When the calculation was performed on a single MB molecule, the MB molecule with the torsion angle of 4.46° was found to be more stable by 1.10 kcal/mol [14]. Next, the energy of MB crystals with the experimental geometry was calculated by the DFT method. The model was comprised of 13 MB molecules (Fig. 2*b*) because at least 12 MB molecules are necessary to surround one MB molecule for performing BSSE calculation. The same

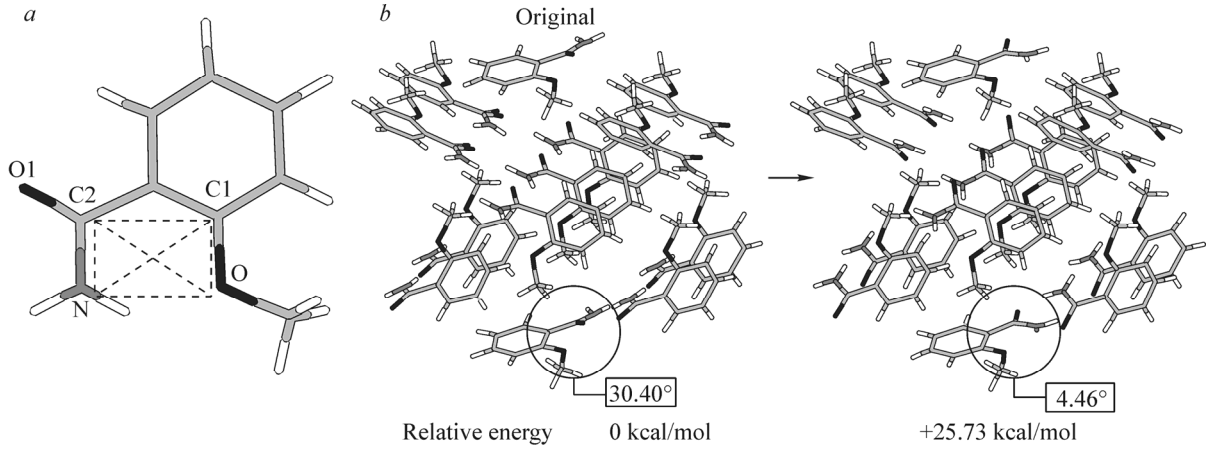


**Fig. 2.** Torsion angle (O–C1–C2–N) of MB (*a*) and the relative energy due to the change of torsion angle (*b*).

calculation was performed using a model in which all of the molecules have their torsion angles reduced from 30.40° to 4.46° (Fig. 2*b*). It was assumed that MB molecules aggregate simply to make a MB crystal. The energy difference was calculated by subtracting the energy value of the latter structure from that of the former one. The difference was estimated to be –25.73 kcal/mol by 13 molecules, indicating that the MB molecules are packed as in crystal with changing their conformation. An MB molecule in an MB crystal interacts with the neighboring MB molecules through four intermolecular hydrogen bonds: two O1···H1–N1 (2.980 Å) and two O1···H2–N1 (2.952 Å). When the torsion angle of all the MB molecules changed from 30.40° to 4.46°, all O1···H1–N1 hydrogen bonds collapsed (3.610 Å), whereas two O1···H2–N1 hydrogen bonds remained (2.969 Å). The interaction energy between one MB and other surrounding MB molecules was calculated to be –10.06 kcal/mol in the real crystal, whereas it was only –3.05 kcal/mol in the model. These results suggest that the lattice energy of MB crystals is lowered by intermolecular hydrogen bond formation among MB molecules with the high torsion angle conformation, which subsequently stabilizes the crystal.

From our previous study, equimolar complexation behavior of urea or thiourea was only observed with compounds with a single 2-alkoxybenzamide structure, such as EB, MB, and 2-methoxybenzhydrazide (data not shown). Though the crystal structure of EB has not been determined yet, EB also seems to have the high torsion angle conformation in the crystals.

**EB–thiourea, MB–thiourea, and MB–urea equimolar complexes.** The interactions between a guest molecule and urea derivatives were evaluated. To simplify further discussions, one host molecule-one guest molecule complexes were considered. We calculated the total energy of each complex structure (EB–thiourea, MB–thiourea and MB–urea) based on crystallographic data as well as on the single structure of guest molecule and host molecule by extracting the complex structure to compare stability (Fig. 3). This interaction energy was derived by subtracting the summation of the energy value of each host and guest molecule from the energy value of host-guest complex. As mentioned in the Experimental section, the energy was corrected by excluding BSSE. As shown in Table 1, the host—guest interaction energy in each system is about 8 kcal/mol. In the case of MB–thiourea complex, another N–H···O=C intermolecular hydrogen bond participates in the complexation, and the interaction energy was –2.43 kcal/mol. The N–H···O=C intermolecular hydrogen bond length was 3.061 Å, which is longer than that of the more stable bond (2.920 Å, Fig. 3*d*). In the EB–thiourea complex, a N–H···O=C intermolecular hydrogen bond (2.984 Å) was observed. The difference of the hydrogen-bonded structure between MB–thiourea and EB–thiourea complexes seems to affect the physicochemical properties of the complexes reported previously [ 13, 14 ].

Equimolar complexation of MB or EB with thiourea is accompanied by the elongation of N–H···S intermolecular hydrogen bond of thiourea molecules. The hydrogen bond length in the crystal was 3.390 Å. The bond length increased on complexation with MB to 3.445 Å or 3.479 Å, and with EB to 3.448 Å or 3.547 Å, which is beyond an effective hydrogen bond length. It appears that the formation of N–H···S hydrogen bonds in the complex of thiourea with MB or EB do not play an important role for complex formation. In the case of the MB–urea complex, N–H···O intermolecular hydrogen bonds between urea molecules were important for complexation (2.997 Å). Three effective hydrogen bonds (N–H···O: 3.022 Å, 3.033 Å, O···H–N:3.000 Å) were observed between urea and MB molecules, which contribute to the stabilization.

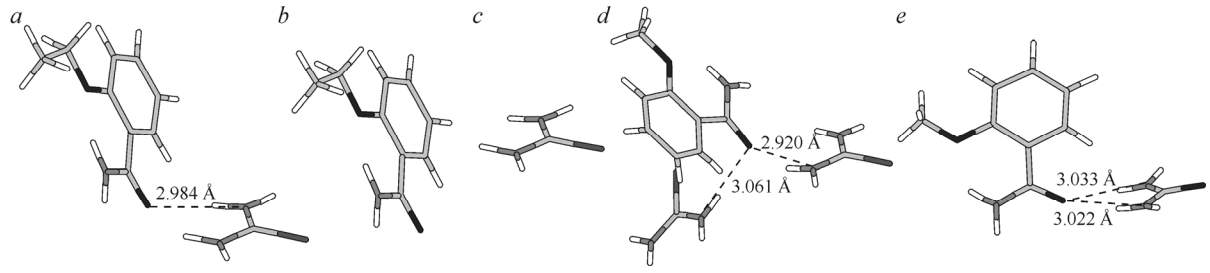


**Fig. 3.** Structures of urea and thiourea complex used for the calculation of interaction energy due to complexation: EB–thiourea complex (*a*), EB (*b*), thiourea (*c*), MB–thiourea complex (*d*), MB–urea complex (*e*).

**TABLE 1.** Interaction Energy (kcal/mol) by Complexation and Changes of Torsion Angle (deg).

| System | Interaction energy due to complexation [a] | Torsion angle of the complex (O–C1–C2–N) | Relative energy when torsion angle changed to 30.40° [a] |
|---|---|---|---|
| MB–urea | –8.19 | 4.46 | +3.42 kcal/mol |
| MB–thiourea | –7.96 | 4.46 | +5.01 kcal/mol |
| EB–thiourea | –8.34 | 1.81 | +2.87 kcal/mol |

[a] Structural differences were shown in Fig. 3.

**Effect of rotation of the amide group of EB or MB on structural stabilization of the equimolar complex with urea or thiourea.** The change of torsion angle between alkoxy C–O and amide C–N bonds on complexation was examined (Fig. 4). The torsion angles of the complexes were shown in Table 1. Since the single crystal structure for EB is not known, we assumed that its original torsion angle equal to that in the MB intact crystal (30.40°). To compare the energies of complexes with high and low torsion angle conformation of MB or EB, the potential energy of the each complex was calculated. The relative energy was obtained by subtracting the energy of high torsion angle conformation of MB (or EB)–urea (or thiourea) complex (Fig. 4*a*) from the energy of low torsion angle conformation of MB (or EB)–urea (or thiourea) complex (Fig. 4*b*). As shown in Table 1, the MB–urea, MB–thiourea and EB–thiourea complexes were destabilized when the torsion angle increased from 4.46° or 1.81° to 30.40°. These results suggest that the complexation occurred because the guest molecule changed into a flattened structure, which is more adapted to form intermolecular hydrogen bond with urea or thiourea. Because urea and thiourea are not as bulky as MB and EB, it would be easy for MB or EB to form flattened conformation when they are packed as in crystal. On the other hand, MB and EB are so bulky that they might adopt a high torsion angle conformation in MB (or EB) single crystal. Steric effects of the amide and methoxy or ethoxy groups, hydrogen-bond donating and accepting capabilities and crystal packing capabilities could be responsible for the twisting configuration of MB or EB molecules. Flattening of MB by the complexation simultaneously satisfies the directional demands of the hydrogen bonds forming between the urea and the MB molecules and the close packing requirements of the crystal lattice.

**Complexation energy of EB–urea equimolar complex.** We simulated an EB–urea complex based on crystallographic structure data of MB–urea (Fig. 5). It was assumed that EB—urea complex has the same configuration as MB–urea complex. Though EB–urea is equimolar complex, the model was constructed by using 8 urea and 6 MB molecules in order to consider hydrogen bond network. At first, we constructed an EB molecule based on the MB structure. Three kinds of elongation of the carbon chains for the 2-alkolxy group of MB were considered as shown in Fig. 6. After the geometry optimization at the B3LYP/6-31G** level, which was performed by fixing the geometry of each molecule, the complexation energy was calculated at the B3LYP/6-31+G** level. The most planar conformation (Fig. 6*a*) was the most stable of the three. We calculated the complexation energy of the optimized EB molecule by subtracting the total energy

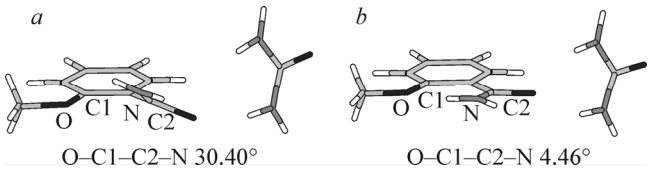


**Fig. 4.** Structure of MB–urea complex used for the calculation of relative energy due to change of torsion angle: high torsion angle conformation (*a*), low torsion angle conformation (*b*).

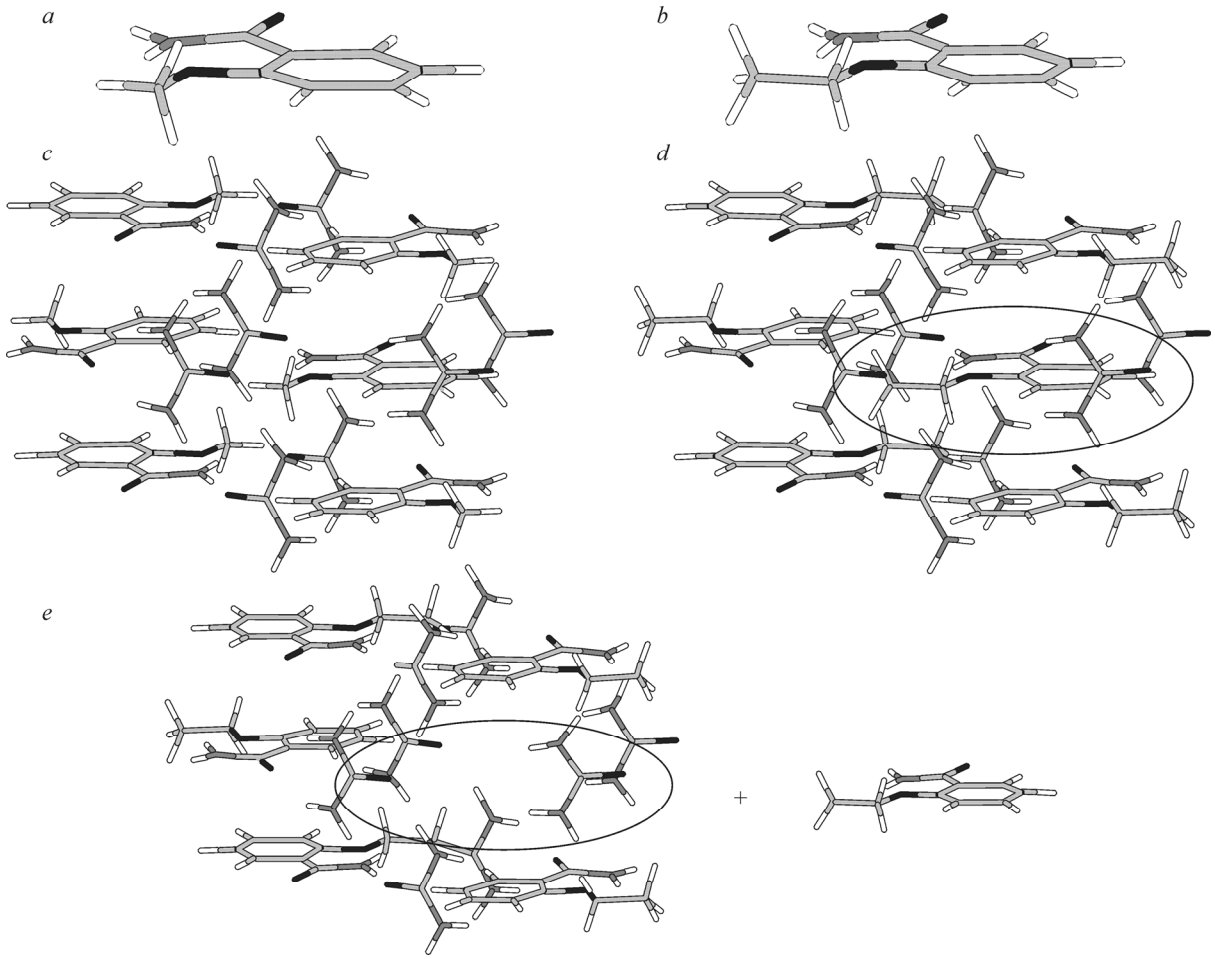


**Fig. 5.** Structure of constructed EB–urea complex based on MB–urea complex: MB (optimized conformation) (*a*), constructed EB (*b*), MB–urea complex (*c*), constructed EB–urea complex (*d*), constructed EB–urea complex + EB (*e*).

value of EB and urea from that of the complex. The obtained energy value was +34.93 kcal/mol, that is, the structure was not stabilized by complexation. The same calculation on MB–urea complex showed the complexation energy was –1.59 kcal/mol. In the case of the MB–urea equimolar complex, the urea hydrogen bond network as well as intermolecular hydrogen bonds between MB and urea were recognized as important to form a urea-drug equimolar complex [14]. Specific conformational changes of MB from the distorted to the flattened structure occurred on the complexation. Steric effects of the amide and methoxy groups, hydrogen-bond donating and accepting capabilities and crystal packing requirement could be responsible for the twisting configuration of MB. In the case of EB–urea complex, elongation of the carbon chains of MB made intermolecular distance between neighboring constructed EB molecules closer as shown in Fig. 7*a* and 7*b*. The EB–EB distances did not change so much by optimization at the DFT level (Fig. 7*c*). On the contrary, the hydrogen bond distance between urea molecules (2.977 Å, 2.997 Å) became closer by the structural optimization (2.834–2.973 Å). Intermolecular interaction between EB and urea molecules slightly changed by the optimization but within the range of effective hydrogen-bond lengths (Fig. 7*d* and 7*e*). The closer packing of the neighboring EB molecules in the EB–urea complex due to bulkier ethoxy group may adversely affect the formation of the complex. For this reason, it would be considered that repulsion of EB molecules occurs which hinders the formation of the EB–urea equimolar complex. Since, experimentally, we have not obtained the EB–urea complex by the co-grinding techniques, the energy calculation method would be a promising method to predict the possibility of EB–urea equimolar complex formation by means of the complexation energy.

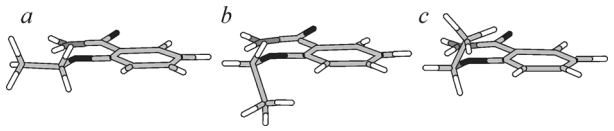


**Fig. 6.** Three kinds of constructed conformation of EB molecule on MB–urea complex.

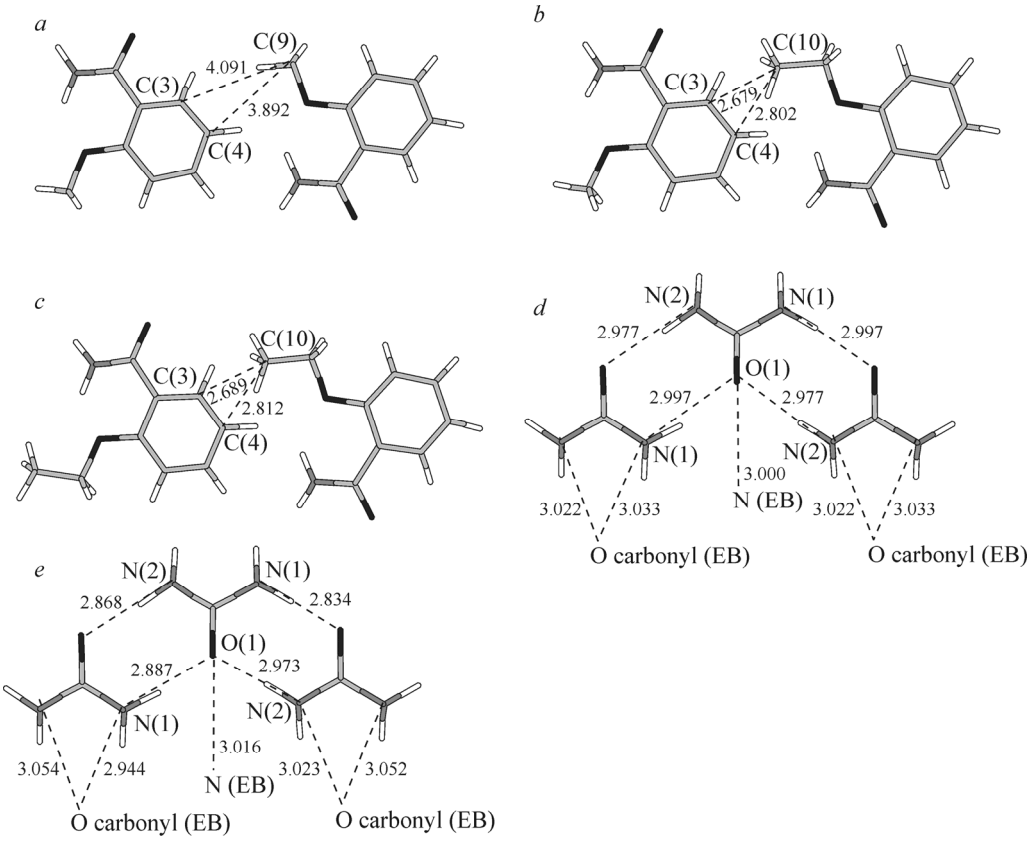


**Fig. 7.** Intermolecular distances between neighboring MB, EB and urea molecules. MB–urea complex (*a*), constructed EB molecules in EB–urea complex before (*b*) and after optimization (*c*), urea molecules in EB-urea complex before (*d*) and after optimization (*e*).

## CONCLUSIONS

Complexation energies of EB–thiourea, MB–thiourea and MB–urea complexes were calculated. It was determined that specific torsion angle (O–C1–C2–N) of the guest molecule in the crystal structures could contribute to the complex formation by co-grinding with urea or thiourea. The complexation energy of the simulated EB–urea complex indicated that urea and EB does not form a complex expected, and it is consistent with experimental results.

The computations were carried out by DRIA system at Graduate School of Pharmaceutical Sciences, Chiba University.

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