

# Theoretical investigation of the lattice energy of urea: Insight from DFT using systematic cluster method

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## Abstract

Lattice energy is the energy needed to form crystals of a compound from the individual molecules. It is related to the stability of a compound in the solid state. In this study, systematic cluster method has been applied to obtain the lattice energy of urea. Using this method, the effect of solid state environment is included in a systematic way. Starting from the small clusters containing a few molecules, the largest cluster we studied contains 84 molecules. In order to improve the results from the cluster method using Gaussian 09 program, correction using the D3BJ program was included. The results show that, when compared to the experimental value, the lattice energies obtained were under-estimated for all the theoretical levels considered. Generally, application of the systematic cluster method shows decrease in calculated lattice energy as more molecules were included in the clusters and becomes closer to the experimental value of urea. Of all the levels considered, B3LYP/DEF2-TZVP with correctional terms provides the closest value to the one from the experiment.

**Keywords:** Systematic cluster method; urea; dispersion correction; lattice energy; geometrical counterpoise.

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## INTRODUCTION

Changes in organic compound's structure and properties affect the handling and processing of the materials, hence control the final product usage (Cruz-Cabeza et al., 2014). The existence of different stable conformers is considered as one of the important occurrence in pharmaceutical and material industries. Ritonavir, an HIV drug widely known as an example of conformational polymorphism, is found to exist in two different forms ("cis" and "trans"). Since "cis" form is more stable than "trans" form but fail to perform as anticipated, it was eventually withdrawn from the pharmaceutical industry (Bauer et al., 2001). Thus, researchers aim to identify low lattice energy conformer as it describes the most stable lattice structure.

In a theoretical study, reliable computational prediction of lattice energy is of crucial importance to simulate the structure of organic compound (Feng et al., 2006). Reliable computational prediction enables the accurate treatment of different types of intermolecular interactions, including electrostatics, induction and dispersion. Kohn-Sham density functional theory (KS-DFT) is a method known to account for electrostatic and induction interactions of molecular crystals (Sousa et al., 2007; Kohn et al., 1996). However, semilocal functionals fail to adequately model the dispersion interaction (Pérez-Jordá et al., 1995). Thus, development of dispersion-including DFT model had gained attention from researchers. Semiclassical dispersion correction is known to be less computationally demanding than other dispersion correction methods (Beran, 2016). This add-on corrections, for example the D3 scheme formulated by Grimme *et al.* (Nangia, 2006), is enough in predicting the organic compound behaviour (Dennington et al., 2006). Further refinement of this method includes

the damping scheme. Similar to D3, this new method, known as D3BJ (Grimme et al., 2011) does not affect the long range decay of the dispersion energy but improves the dispersion energy decays to zero at short range part of D3. D3BJ has proven its reliability as it gives less average error compared to non-dispersion corrected calculation and D3 dispersion-corrected DFT scheme (Grimme et al., 2011; Christensen et al., 2016). Hence, D3BJ is preferred over D3 scheme.

Crystalline solid is structured from an infinite number of molecules which include the intermolecular interaction effects from the neighbouring molecule. Thus, to elucidate this environment, the interactions between neighbouring molecules have to be considered. However, supramolecular approach usually has the basis set superposition error (BSSE) due to unbalanced basis set expansion of monomer. The counterpoise (CP) scheme by Boys and Bernardi can be used for this problem (Boys et al., 1970) but it only considers intermolecular BSSE of non-covalently bound dimer complexes. Another scheme, known as geometrical counterpoise (gCP), offers estimation of the inter- and intra-molecular BSSE for DFT calculations with various basis sets (Kruse et al., 2012). gCP estimates the correction only based on the cartesian coordinates of the molecules or complexes.

## EXPERIMENTAL

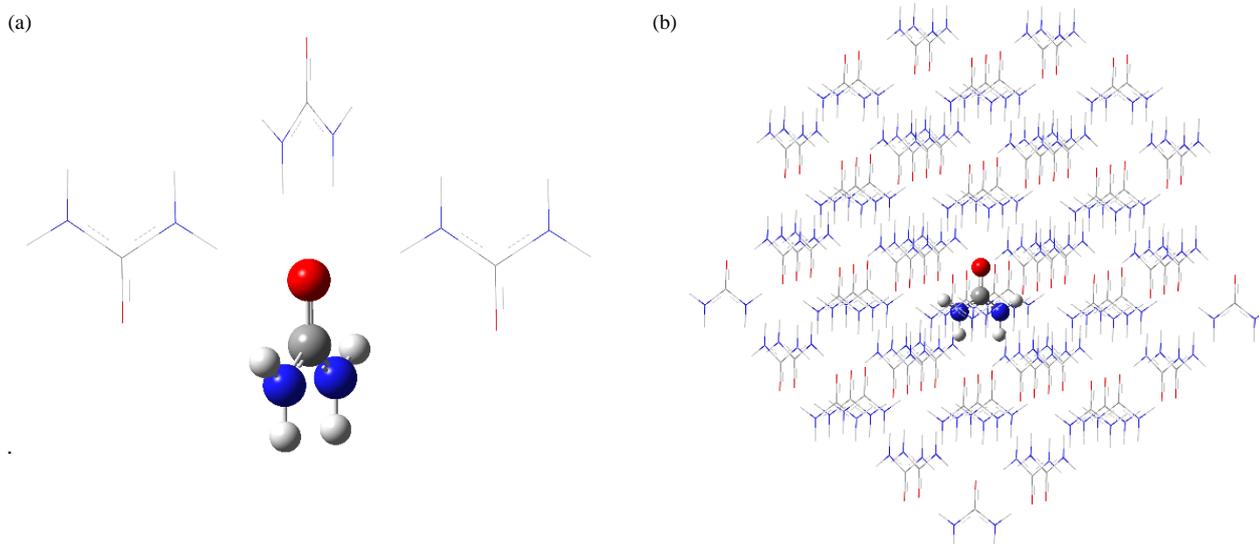
In this study, systematic cluster calculations were performed on clusters with increasing number of molecules. Coordinates of urea are generated with 1Å increment starting from 3Å distance as shown in Figure 1(a) (excluding one-molecule and dimer cluster) until 10Å distance (Figure 1(b)). This study produced a total of 10 clusters

(including one-molecule and dimer cluster) with the largest contains 85 molecules of urea. Thus, this cluster is considered to represent better the intermolecular energy and mimics the solid state environment compared to the used of small-sized clusters. The coordinates used for urea molecules were obtained from Crystallography Information File through the Cambridge Structural Database (CSD) (Zavodnik et al., 1999). Official CSD visualizer program, Mercury (Macrae et al., 2008) was utilized to generate the coordinates of the cluster molecules.

Theoretical calculations were performed with Gaussian 09 suite of program by utilizing DFT at B3LYP level of theory with DEF2-TZVP as the basis set (Frisch et al., 2009). The scheme known as D3BJ (Grimme et al., 2011) was used for the calculation of the dispersion energy, while for BSSE correction, gCP scheme (Kruse et al., 2012) was used. Results were visualized with GaussView 4.1 (Dennington et al., 2006).

Total energy is described as

$$E_{\text{total}} = E_{\text{scf}} + E_{\text{GD3BJ}} + E_{\text{gCP}} \quad (1)$$



**Figure 1** Clusters of urea: (a) four-molecule cluster and (b) 85-molecule cluster. Colours for the elements are red for oxygen, grey for carbon, blue for nitrogen and white for hydrogen. The centre/initial molecule is displayed with ball and stick form, while the neighbouring molecules are in wireframe form.

## RESULTS AND DISCUSSION

The results of the systematic cluster calculations are tabulated in Table 1 and graphically displayed in Figure 2. Results show that for all the methods considered, the relative energy,  $E_{\text{rel}}$  is decreasing (becoming more negative) closer to the experimental value as the number of molecules increases. The trend of the graph shows a decrease in gradient of within the last four points than at initial point of cluster. Some fluctuations can also be seen at the beginning of the graph.

According to Equation 2, relative energy is from the difference between  $\frac{E_{\text{total}}}{n}$  with  $E_{\text{molecule}}$ , where  $\frac{E_{\text{total}}}{n}$  is an average energy of each molecule in clusters. As we adopt the systematic cluster method, increment number of molecules was considered systematically according to distance from central molecule. Intermolecular interaction (interaction between molecules) for inner molecules differs from outer molecules.

From Figure 3, center molecule (ball and stick form) will have interaction with neighbouring molecules surrounding it while outer molecule (stick form) only has interaction of inner molecules. This

where  $E_{\text{total}}$  is the total energy of the cluster which includes the corrective energies of dispersion ( $E_{\text{GD3BJ}}$ ), BSSE ( $E_{\text{gCP}}$ ) and  $E_{\text{scf}}$  is the self-consistent field energy from Gaussian 09. The relative stability of the clusters is assessed by using the criterion of relative energy with equation

$$E_{\text{rel}} = \frac{E_{\text{total}}}{n} - E_{\text{molecule}} \quad (2)$$

where  $n$  is the number of molecules in the cluster and  $E_{\text{molecule}}$  is the energy of the single molecule.

In this study, compound of interest is urea. It is a simple molecule that has been the subject of many experimental and theoretical studies (Spoliti et al., 1997; Civalleri et al., 2007). Experimental lattice energy ( $99.43 \text{ kJ mol}^{-1}$ ) from Otero-de-la-Roza and Johnson (William Acree et al., 2010) is used as reference for comparison with the theoretical study.

explains the fluctuation at the beginning of the graph. At larger number of molecules, systems start to possess the solid state environment for the center molecule where the outer molecules have less effect on the overall system's interaction (William Acree et al., 2010). Thus, more consistent graph can be visualized in Figure 2 at larger number of molecule clusters. Even though  $\frac{E_{\text{total}}}{n}$  is affected

by dispersion or BSSE correction scheme, both graphs with or without correction have the same pattern, hence, in conclusion, still remains the same with or without correction.

Inclusion of the dispersion correction and gCP scheme in molecule is also presented in Figure 2. We found that with inclusion of the dispersion corrections,  $E_{\text{rel}}$  is more negative than those without, (where in our notations is more stable). As D3BJ has negative values, the net result is the increased cohesiveness of the molecules. Hence, the inclusion of the correction schemes gave a more strongly bounded picture for the molecules. However, as the gCP is included, result shows the relative energy was high-shifted compared to the dispersion correction result.

**Table 1** Energies of urea clusters; (a) without dispersion correction, (b) with dispersion correction (D3BJ), and (c) with dispersion correction (D3BJ) and BSSE correction (gCP).

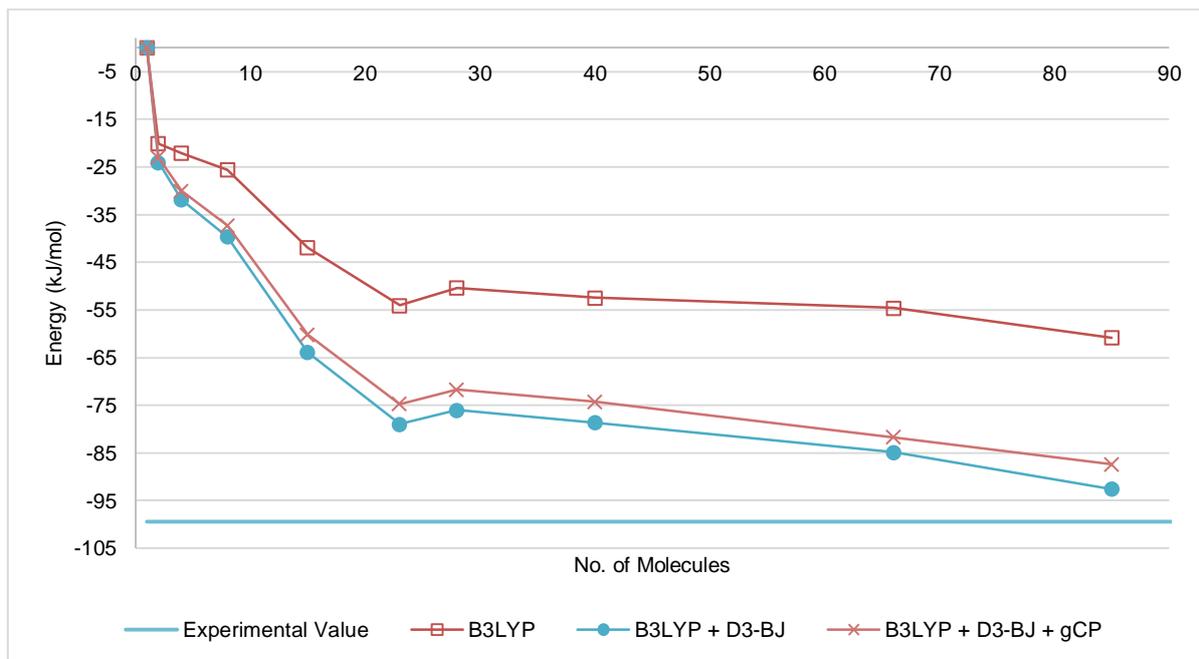
(a)			
Molecules in cluster, $n$	$E_{\text{total}}$ (Hartree)	$\frac{E_{\text{total}}}{n}$ (kJ/mol)	$E_{\text{rel}}$ kJ/mol)
1	-225.36652894	-591699.82173722	0.00000000
2	-450.74836946	-591719.92200468	-20.10026746
4	-901.49983138	-591721.95181942	-22.13008220
8	-1803.01027566	-591725.43484317	-25.61310595
15	-3380.73754187	-591741.76107865	-41.93934142
23	-5183.90344929	-591753.84809178	-54.02635456
28	-6310.79984084	-591750.17793305	-50.35619583
40	-9015.46042661	-591752.28375161	-52.46201439
66	-14875.56243300	-591754.38133093	-54.55959371
85	-19158.12296360	-591760.60989346	-60.78815624

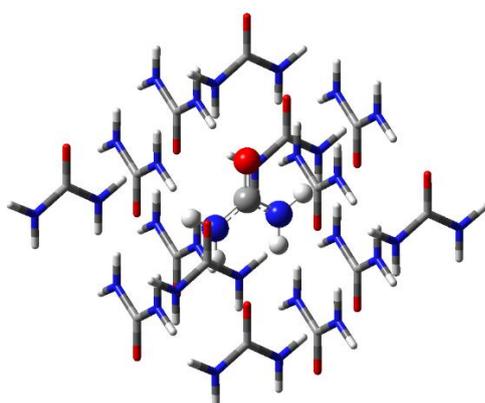
(b)			
Molecules in cluster, $n$	$E_{\text{total}}$ (Hartree)	$\frac{E_{\text{total}}}{n}$ (kJ/mol)	$E_{\text{rel}}$ (kJ/mol)
1	-225.37397362	-591719.36774981	0.00000000
2	-450.76624351	-591743.38616250	-24.01841269
4	-901.54448829	-591751.26350201	-31.89575219
8	-1803.11258330	-591759.01093177	-39.64318196
15	-3380.97456973	-591783.24885507	-63.88110526
23	-5184.29341456	-591798.36347510	-78.99572529
28	-6311.28178571	-591795.36887077	-76.00112096
40	-9016.15636330	-591797.96329610	-78.59554629
66	-14876.81587780	-591804.24374491	-84.87599510
85	-19159.78416070	-591811.92134021	-92.55359040

(c)			
Molecules in cluster, $n$	$E_{\text{total}}$ (Hartree)	$\frac{E_{\text{total}}}{n}$ (kJ/mol)	$E_{\text{rel}}$ (kJ/mol)
1	-225.36902464	-591706.37418051	0.00000000
2	-450.75559197	-591729.40335297	-23.02917247
4	-901.52193858	-591736.46243788	-30.08825737
8	-1803.06577452	-591743.64887663	-37.27469612
15	-3380.87944898	-591766.59955303	-60.22537252
23	-5184.14209264	-591781.08974943	-74.71556892
28	-6311.09753952	-591778.09250048	-71.71831997
40	-9015.89232803	-591780.63268116	-74.25850065
66	-14876.40987421	-591788.09279921	-81.71861870
85	-19159.19577004	-591793.74699110	-87.37281059

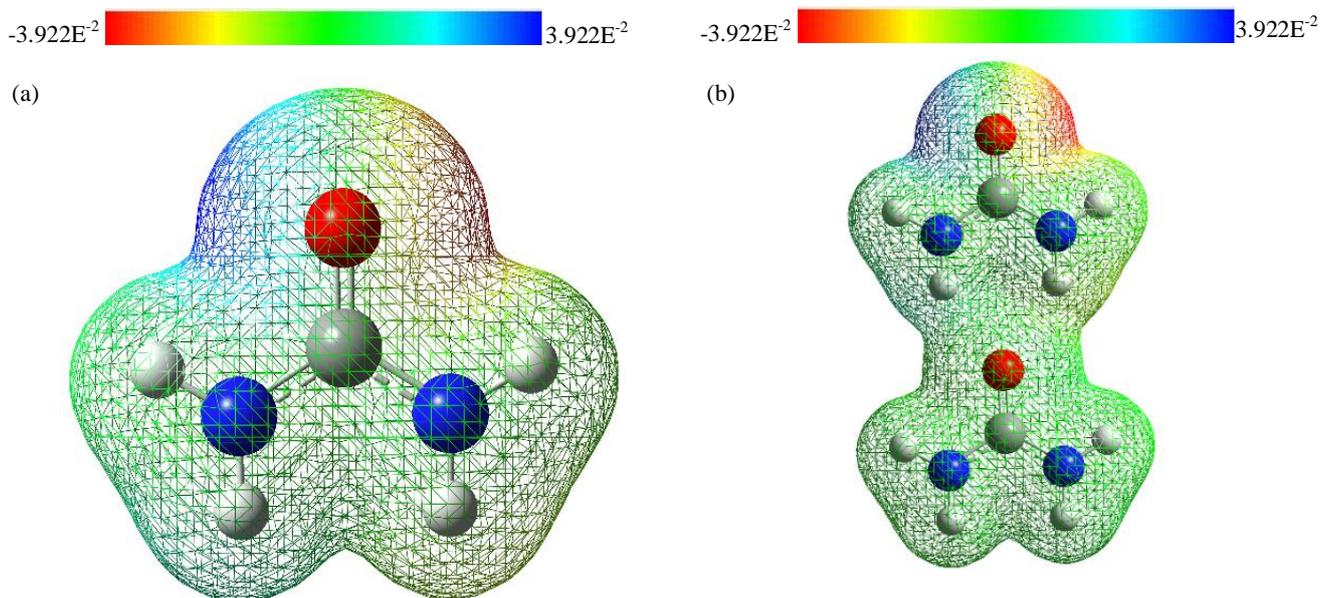


**Figure 2** Calculated lattice energy of urea. Experimental value for urea is 99.43 kJ/mol. The lines connecting the dots are drawn to visualize better the variations of the energies.



**Figure 3** 15-molecule cluster of urea.

Figure 4 shows the mapped surface of HOMO and electron density with density isovalue  $0.004 \text{ e/au}^3$ . This MEP mapped surface is related to the electronic density and descriptor for determining sides for electrophilic and nucleophilic reactions (Sendil et al., 2016). The colour denotes the reactivity of the region; blue is most positive electrostatic potential, red is most electronegative electrostatic potential and green represents regions of neutral potential. As shown in Figure 4(a), for one-molecule urea the reactive region is at the oxygen of the molecule. Same reactive region is shown for MEP surface of two-molecule ureas. However only the top molecule has reactive region while the bottom one is totally green which shows that the bottom molecule is not reactive. Compared to Figure 2, the two-molecule ureas is more stable since only one molecule has a reactive side while the other molecule has not. Thus, the average energy for a dimer is lower than that of a one-molecule urea. Same situation describes the decrement of urea energy as number of molecule increases.



**Figure 4** The molecular electrostatic potential (MEP) maps for (a) one-molecule (b) two-molecule urea. The colour bars are the indicator for the potentials (in au).

## CONCLUSION

We presented the applications of the systematic cluster method with the dispersion and BSSE correction effect included. Systematic increase in the number of molecules shows the effect of inter- and intramolecular interaction to the cluster molecule. At larger number of molecules, energy was more consistent and stable to mimic the solid state environment. The stability of urea molecule was also studied from the aspects of molecular orbitals and electron distributions. Our results show that the inclusion of the D3BJ and gCP correctional schemes is preferable for lattice energy calculations.

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