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Role of hydrogen bonding in conformational energies of hexachlorophene and its derivatives - A theoretical study

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Received 11 October 2017; re-revised and accepted 25 April 2018

Conformational space around two dihedral angles (viz., θ and ϕ) in hexachlorophene (HCP), dimethylhexachlorophene (DMHCP) and diphenylhexachlorophene (DPHCP), has been scanned at the AM1 level and further the minima optimized at DFT(B3LYP)/6-31G(d) level. All possible hydrogen bonds that may exist in these molecules in different conformations, have been explored. NBO analyses have been carried out to establish the role of hydrogen bonds in resolving the energies of conformers.

Keywords: Theoretical chemistry, Density functional calculations, Conformational energy, Intramolecular hydrogen bonding, Hexachlorophene

Hexachlorophene, 2,2'-methylenebis(3,4,6-trichlorophenol) (HCP) is an organic compound which is widely used as a disinfectant, antibacterial agent, ticide for poultry, fasciolicide for cattle, germicidal agent in soaps and dermatological preparations¹. In general, chlorinated bisphenol is an antiseptic with a bacteriostatic action and so HCP is used as a preoperative hand scrub by health-care personnel to prevent spreading of cutaneous microorganisms from hands and forearms during surgery². It also plays a vital role in agriculture as a fungicide to treat various citrus fruits and vegetables³, plant bactericide, soil fungicide, pesticide and acaricide⁴⁻⁶. Further, it is known that HCP is applied to barley at the beginning of the malting process to stimulate rootlet growth⁷.

A fine relationship exists between the structure and bioactivity of a compound. Hydrogen bonding is the most important force contributing to the structural/conformational stability⁸. The formation of intramolecular hydrogen bonds in biological and synthetic systems have a pronounced effect on molecular structure, properties and biological activities⁹⁻¹¹. There are kinetic evidences supporting the formation of intramolecular hydrogen bonding in HCP and HCP monoacetate^{12,13}. Further, HCP is known

to bind to adjacent sites in bacterial Enoyl-ACP Reductase (FabI). Hence, conformational study was considered suitable for studying the interaction of HCP with the enzyme, and is reported at the restricted Hartree-Fock (RHF) level^{14,15} of theory and using density functional theory¹⁶⁻¹⁹ (DFT) with the functional B3LYP and the 6-31G(d) basis set.

In the present study, we have computed the different conformations of HCP at the 6-31G(d) level to investigate the role of hydrogen bonds in determining the energetics of the conformers. We have analysed all the types of intramolecular hydrogen bonding, including O-H.....Cl (within the phenyl rings) (Fig. 1(b)), which has been considered in an earlier report¹⁴ and O-H.....O and O-H.....Cl bonds between the two phenyl rings (which to the best of our knowledge not reported for HCP in literature so far) (Fig. 1(c & d)). In addition we have studied the effect of bulky substituents on the methylene carbon on conformation stability. Herein, we have explored the conformational space of hexachlorophene (HCP), dimethylhexachlorophene (DMHCP) and diphenylhexachlorophene (DPHCP) and the extent to which they are affected by hydrogen bonding.

Computational methods

Geometry of HCP and its dimethyl and diphenyl derivatives, were optimized using Gaussian 98

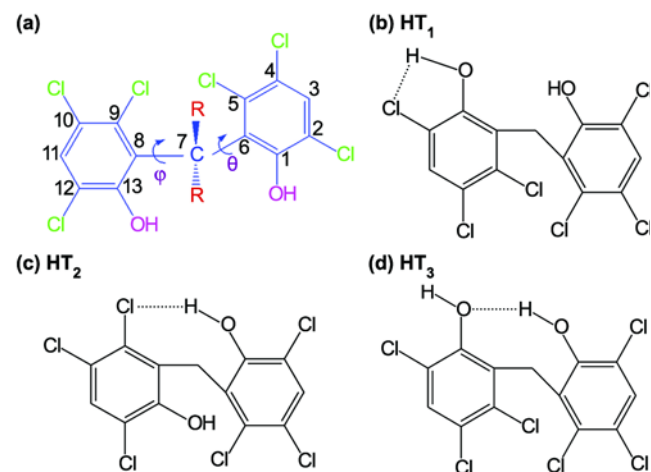


Fig. 1 — Intramolecular hydrogen bonding in HCP and its derivatives. [(a) R = H, HCP; R = CH₃, DMHCP; R = C₆H₅, DPHCP. Dihedral angle θ = C1-C6-C7-C8, ϕ = C6-C7-C8-C13; (b) HT₁; (c) HT₂; (d) HT₃].

program²⁰. The reported molecules map a conformational space due to the two principal dihedral angles, i.e., θ and φ (Fig. 1(a)). Conformation scanning was carried out by varying the dihedral angles, θ and φ , by 30° at AM1 level²¹ for all the three systems. This provided a better initial estimation for the desired minima in the conformational space. Further optimizations were performed for the minima at DFT(B3LYP)/6-31G(d) level²²⁻²⁴. NBO analyses were performed at the same level²⁵.

Results and discussion

Conformational space of the title molecules were mapped as contour plots. The plots were obtained by varying θ and φ (by 30°) and the resulting energy is plotted against θ and φ in the form of contours (Fig. 2). The conformers which were found to have minimum energy according to the contour plots were subjected to optimization at DFT(B3LYP)/6-31G(d) level. The conformers have been designated on the basis of dihedral angles and the type of hydrogen bonding present in the minimum energy conformers are as follows:

Angles (θ, φ) ($^\circ$)	Conformer	Type of hydrogen bonding	Notation
$\geq +60$	g+ (gauche)	O-H.....Cl within the phenyl rings	HT ₁
≥ -60	g- (gauche)		
+100 to +180	a (anti)	O-H.....Cl between two phenyl rings	HT ₂
-100 to -180	a (anti)	O-H.....O between two phenyl rings	HT ₃

The relative energies of all the minimum energy conformers (stabilised by hydrogen bonds under the type specified) of HCP, DMHCP and DPHCP and their

relative Boltzmann population is presented in the same Table 1. The conformers are labelled according to the dihedral angles θ and φ . From the table, it is evident that the substitution of hydrogens in HCP has considerably altered the energies of conformers, and hence, the relative population of each conformer.

For HCP, the lowest energy conformer is (a,g+) ($\theta = -117$; $\varphi = 53$) and the other two conformers (a,a) ($\theta = 123$; $\varphi = 123$) and (g-,a) ($\theta = -59$; $\varphi = 106$) have values comparable to the lowest energy conformer in terms of both energy and population. However, (g+,g+) ($\theta = 55$; $\varphi = 55$) is of slightly higher energy (5.29 kcal/mol). Although all the conformers are stabilized by hydrogen bonds, a variation in their energy values is noted. This could be attributed to the strength of hydrogen bonds and other factors which is discussed subsequently.

In the case of DMHCP, the methyl substitution has played a role in influencing the energies of the conformers. Although there is not much change in the relative energies of the lowest energy conformer (a,a) and the next lowest energy conformer (g-,a) (in comparison to HCP), the energy of (a,g+) is at a higher relative energy than that in HCP, while the (g+,g+) conformer is the highest energy minima with maximum relative energy as in the case of HCP. This energy distribution signifies that upon dimethyl substitution, the system tends to populate with (a,a) (74%) and (g-,a) (25%). This shows the electronic and/or steric effects of the substituent in determining the strength of hydrogen bonding.

Further, the phenyl substitution in DPHCP has also modified the conformational energies making the (g-,a) conformer as the minima. The other three conformers are within an energy difference of

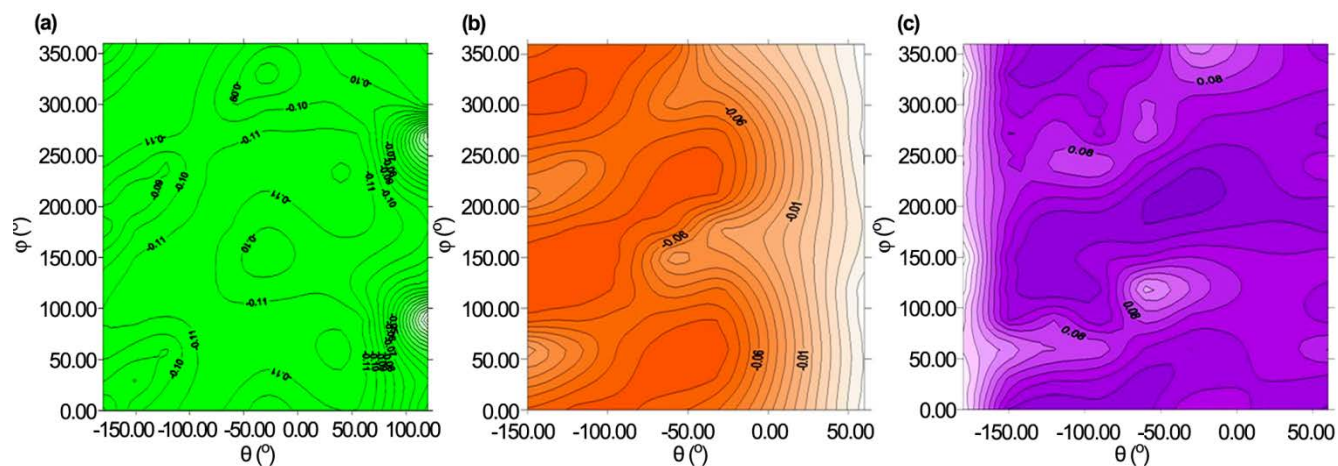


Fig. 2 — Contour plots of (a) HCP, (b) DMHCP, and, (c) DPHCP by variation of angles θ and φ by 30° .

3 kcal/mol. Although the phenyl substitution has changed the lowest energy conformer, all the conformers of DPHCP are of similar conformational energies. Of course the energies of (a,a) and (a,g+) conformers are not affected much, but the energy of (g+,g+) (which was 5.29 in HCP and 5.67 kcal/mol in DMHCP) is nearly halved. This could be due to the variation in strength of the hydrogen bond.

The notable conformational energy difference and dynamics afforded to these molecules is due to the

possibility of hydrogen bonding during different orientations. The H...Cl/H...O distances (Å) are presented in Figs 3–5, showing the proximity of the hydrogen bonding partners. Since the hydrogen bond distance is an inverse function of stability, more the distance, more will be the conformational relative energy and the conformer would be placed at a higher energy level. A correlation graph was plotted between the average of hydrogen bonding distances (as there are two hydrogen bonds the average of their distance is

Table 1 — Relative energy, dihedral angles (θ , ϕ) and % population of HCP, DMHCP and DPHCP

Conformer	Relative energy (kcal/mol)	θ ($^\circ$) ^a C1-C6-C7-C8	ϕ ($^\circ$) ^a C6-C7-C8-C13	Population ^b (%)
HCP (a, g+)(HT ₁)	0	-117	53	53
HCP (a,a)(HT ₁)	0.32	123	123	31
HCP (g-,a)(HT _{1,3}) ^c	0.75	-59	106	15
HCP (g+,g+)(HT ₂)	5.29	55	55	0.007
DMHCP (a,a)(HT ₁)	0	132	132	74
DMHCP (g-,a)(HT _{1,3}) ^c	0.63	-54	118	25
DMHCP (a,g+)(HT ₁)	3.60	-129	52	0.17
DMHCP (g+,g+)(HT ₂)	5.67	54	54	0.005
DPHCP (g-,a)(HT _{1,3}) ^c	0	-60	110	87
DPHCP (a,a)(HT ₁)	1.32	120	120	9.4
DPHCP (a,g+)(HT ₁)	2.14	-117	58	2.3
DPHCP (g+,g+)(HT ₂)	2.82	64	64	0.75

^aFor numbering refer to Fig. 1.

^bBoltzmann populations (%) calculated as $P_i = \exp(-\Delta G_i/kT) / \sum_j \exp(-\Delta G_j/kT) \times 100$, where $k = 1.3806 \times 10^{-23} \text{ J K}^{-1}$; $T = 298 \text{ K}$.

^cHT_{1,3} denotes the H-bond types 1 and 3, coexisting in g-, a conformer.

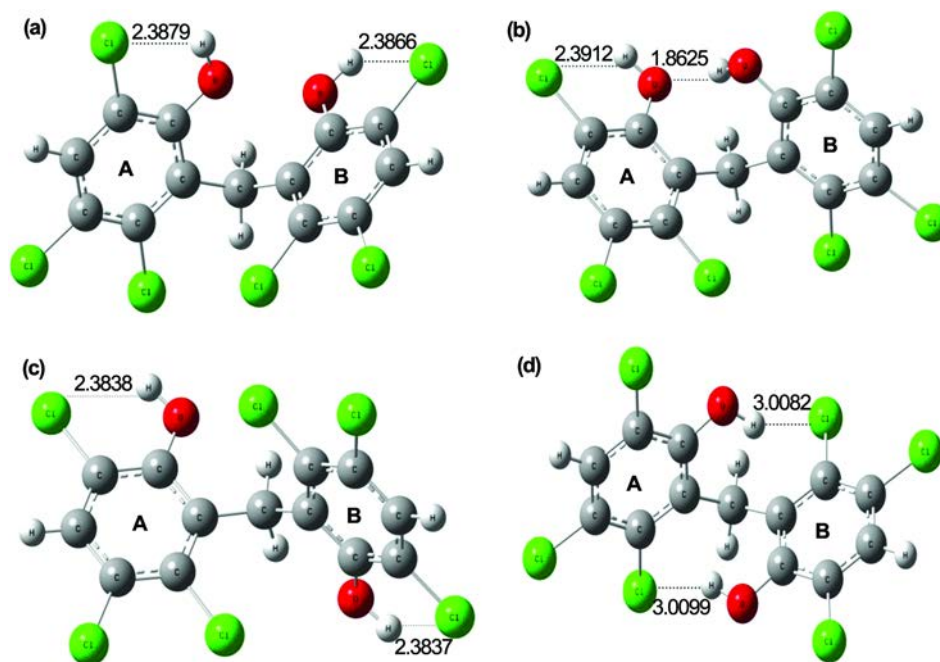


Fig. 3 — Optimized geometries of HCP at DFT(B3LYP)/6-31G(d). [(a) HCP(a,g+) (HT₁); (b) HCP(g-,a) (HT_{1,3}); (c) HCP(a,a) (HT₁); (d) HCP(g+,g+) (HT₂). A and B are two phenyl rings of the title molecules. Distance between hydroxyl proton and chlorine/oxygen is given in Å].

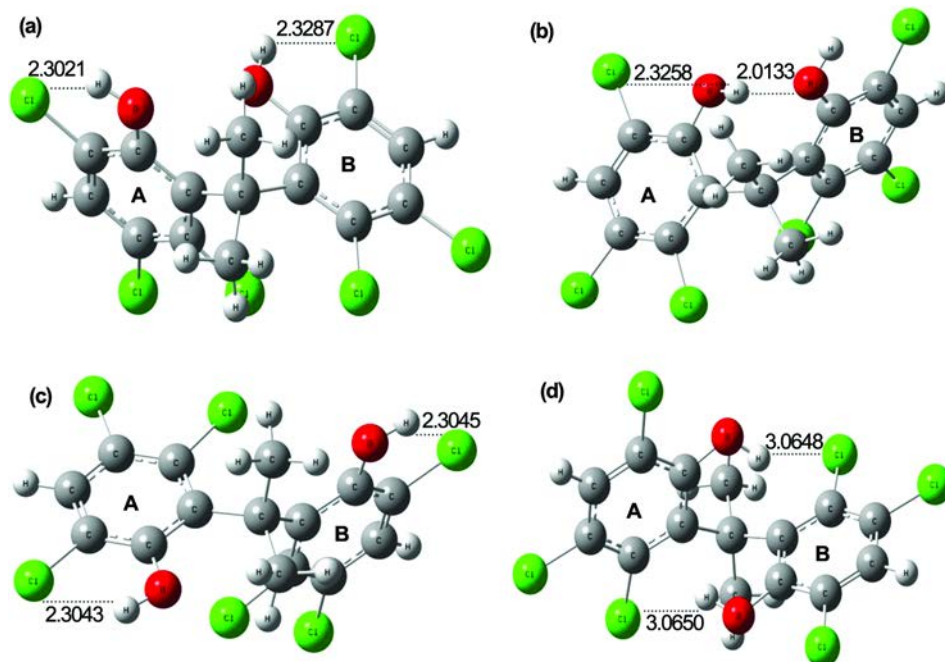


Fig. 4 — Optimized geometries of DMHCP at DFT(B3LYP)/6-31G(d). [(a) DMHCP(a,g+) (HT_1); (b) DMHCP(g-,a) ($HT_{1,3}$); (c) DMHCP(a,a) (HT_1); (d) DMHCP (g+,g+) (HT_2). A and B are two phenyl rings of the title molecules. Distance between hydroxyl proton and chlorine/oxygen is given in Å].

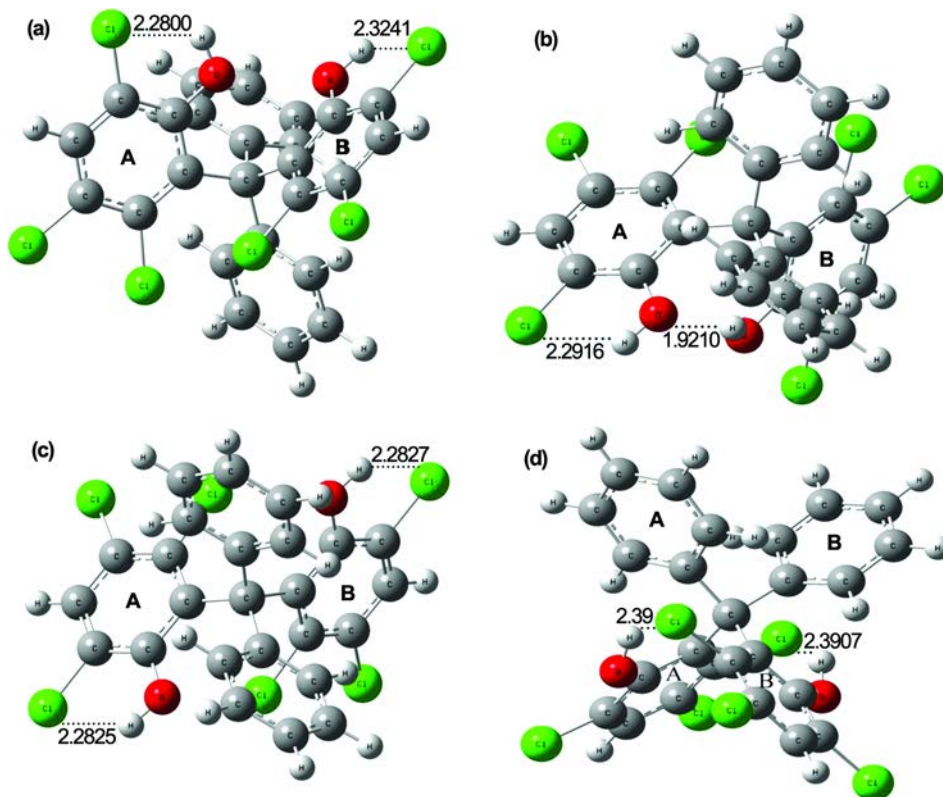


Fig. 5 — Optimized geometries of DPHCP at DFT(B3LYP)/6-31G(d). [(a) DPHCP (a,g+) (HT_1); (b) DPHCP(g-,a) ($HT_{1,3}$); (c) DPHCP(a,a) (HT_1); (d) DPHCP(g+,g+) (HT_2). A and B are two phenyl rings of the title molecules. Distance between hydroxyl proton and chlorine/oxygen is given in Å].

considered here) and the relative energies of the conformers (Fig. 6). It was found that a moderate correlation is obtained when all the systems were taken cumulatively ($R^2 = 0.69$) (Fig. 6(a)). However, when conformers of each system are considered separately, the correlation is found to be good for HCP ($R^2 = 0.813$) (Fig. 6b) and excellent for DPHCP ($R^2 = 0.952$) (Fig. 6d) and fair for DMHCP ($R^2 = 0.696$) (Fig. 6c). This suggests that for HCP and DPHCP, the role of hydrogen bonding in stabilizing the conformer is more significant than other factors (viz., steric, inductive, etc.). This discussion is further confirmed by the additional proof obtained from NBO analysis.

Natural bond orbital analysis is an efficient method to investigate the intra- as well as inter-molecular bonding and interaction of bonds between various atoms. It also provides a convenient basis for exploring charge transfer or conjugative interactions in molecular systems²⁵⁻²⁷. The second order perturbation analysis performed by NBO calculations shows the stabilisation afforded to the systems by the interacting orbitals²⁸. The interactions showing the hydrogen bonding are predominantly those between lone-pair of the donor orbital (O or Cl) and acceptor orbital (σ^*) of O-H which are presented in Table 2. It is seen that in HCP, the (a,g+), (g,a) and (a,a) conformers show LP Cl \rightarrow σ^* O-H interactions while the (g-,a)

Table 2 — Selected data of second-order perturbation energies (E2) of the conformers under study

Donor \rightarrow Acceptor ^a	E2 (kcal/mol)											
	HCP	HCP	HCP	HCP	DMHCP	DMHCP	DMHCP	DMHCP	DPHCP	DPHCP	DPHCP	DPHCP
	(a,g+) HT ₁	(g-,a) HT _{1,3} ^b	(a,a) HT ₁	(g+,g+) HT ₂	(a,g+) HT ₁	(g-,a) HT _{1,3} ^b	(a,a) HT ₁	(g+,g+) HT ₂	(a,g+) HT ₁	(g-,a) HT _{1,3} ^b	(a,a) HT ₁	(g+,g+) HT ₂
LP(1)Cl \rightarrow σ^* O-H (A)	-	-	-	-	-	-	-	-	0.54	0.52	0.54	-
LP(2)Cl \rightarrow σ^* O-H (A)	4.08	4.09	4.12	-	5.63	4.59	5.55	-	5.95	4.85	5.7	2
LP(3)Cl \rightarrow σ^* O-H (A)	-	-	-	-	-	-	-	-	-	1.03	-	2.43
LP(2)Cl \rightarrow σ^* O-H (B)	4.08	-	4.12	-	5.13	-	5.56	-	5.03	-	-	2
LP(3)Cl \rightarrow σ^* O-H (B)	-	-	-	-	-	-	-	-	-	-	-	2.45
LP(1)O(A) \rightarrow σ^* O-H(B)	-	5.17	-	-	-	2.36	-	-	-	4.39	-	-
LP(2)O(A) \rightarrow σ^* O-H(B)	-	7.33	-	-	-	3.86	-	-	-	3.98	-	-

^a(A) and (B) are two phenyl rings of the title molecules.

^bHT_{1,3} denotes the H-bond types 1 and 3, coexisting in g-, a conformer.

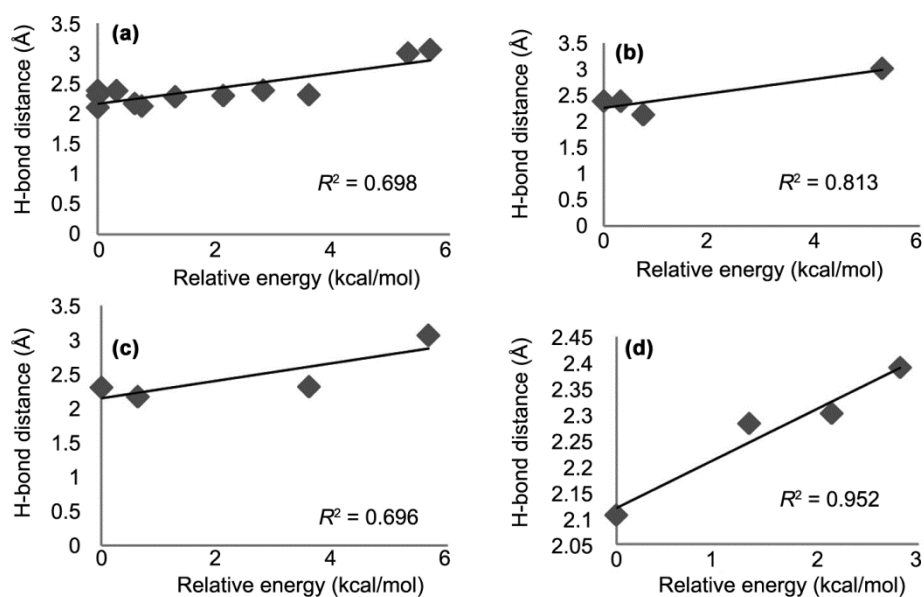


Fig. 6 — Correlation plots between hydrogen bond distance and relative energy of the studied conformers. [(a) Cumulative correlation; (b) correlation for HCP; (c) correlation for DMHCP; (d) correlation for DPHCP].

shows LP O \rightarrow σ^* O-H interactions. This supports the presence of hydrogen bonding in the above conformers. This is not only true for HCP but also for DMHCP and DPHCP. Yet another interesting observation noted here is that, the (g+,g+) conformers of HCP and DMHCP do not show such interactions which explains their high relative energy. On the other hand, the (g+,g+) conformer of DPHCP exhibits the above said interactions which is reflected in its low relative energy. In contrast to other (g+,g+) conformer, the relative energy of DPHCP (g+,g+) is nearly halved, the clear reason being the hydrogen bonding. The hydrogen bonding was possible due to the H...Cl proximity (Fig. 5) that was afforded by the space effect due to phenyl substitution. This again adds to the already established excellent correlation between the average hydrogen bond distance and relative energies (Fig. 6). These factors show the role of hydrogen bonding as the predominant force that decides the conformation energies which may be additionally reinforced or sometimes reduced by the electronic and steric effects of the substituents.

In conclusion, the free rotation of θ and ϕ dihedral angles in hexachlorophene and its derivatives result in four notable minimum energy conformers (viz., a,g+; a,a; g-,a; g+,g+). The delicate conformational flipping is seen to be influenced dominantly by the hydrogen bonds present in them, yet the steric role of substituents cannot be neglected. Existence of LP \rightarrow σ^* interactions evidenced by $E(2)$ energies of NBO analysis and good correlations support the hydrogen bonding and their role in conformational stability.

Acknowledgement

LA thanks the University Grants Commission, New Delhi, for the financial assistance through minor research project (No. F-MRP6409/16(SERO/UGC)).

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