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Distinction between low-barrier hydrogen bond and ordinary hydrogen bond: a case study of varying nature of charge assisted hydrogen bonds of diglycine perchlorate crystal

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Abstract

Hydrogen bonding is a complex phenomenon that is a resultant of many energy components like the electrostatic, dispersive, covalent, charge cloud overlap repulsion etc, nature of hydrogen bond (H-bond) depends on which of these components play a dominant role. Low barrier hydrogen bond (LBHB) constitutes a special category of hydrogen bonds characterized by near delocalization of proton between donor and acceptor groups of the H- bond unlike an ordinary hydrogen bond (OHB) having proton clearly localized near the donor group. The significance of LBHBs in macromolecular interactions has been highly controversial, despite may attempts the existence and potential importance of protein LBHBs remains debatable. In order to answer questions like whether or not a distinct class of LBHBs exists and if they do exist under what conditions they are formed and how do they behave differently from OHBs, a detailed study of H-bonding in Diglycine Perchlorate (DGPCl) crystal containing five unique hydrogen bonded glycinium-glycine pairs is undertaken. All O-H–O bonds of DGPCl are between the carboxyl (-COOH) and carboxylate (-COO^-) groups with slightly different electron distributions resulting in observable variations in the H-bond geometries, this is an indication of varying strength of these short strong H-bonds. It is found that LBHB nature of the five O-H—O bonds between glycinium-glycine pairs (P1-P5) varies as $P1 < P4 < P2 < P3 < P5$. This study gives an experimental evidence of the existence of LBHBs and demonstrates that the behaviour of LBHBs is very different from that of strong OHBs.

Introduction

Hydrogen bonds are arguably the most enigmatic and versatile intermolecular interactions [1], they play a fundamental role in biochemical processes hence in order to understand the biophysical systems it becomes important to study the nature of these interactions minutely. Nature of hydrogen bonds particularly the strong ones is complex, it is a resultant of many interactions like the electrostatic, dispersive, covalent, charge cloud overlap repulsion etc Low barrier hydrogen bond (LBHB) constitutes a special category of hydrogen bonds characterized [2, 3] by near delocalization of proton between donor and acceptor groups of the hydrogen bond, it is assumed that potential energy landscape for these hydrogen bonds has a double minimum form where the barrier height between the two minima is of the order of zero point energy of the proton. Role of LBHB in enzyme studies is an ongoing topic of interest, as LBHB has been proposed to play a major factor in enzyme catalysis through transition state stabilization; these hydrogen bonds can also play a role in proton conductivity within molecular clusters. In order to consider LBHB as a distinct class of hydrogen bond they should have some unique characteristic not present in ordinary hydrogen bonds (OHB) that have proton clearly localized near the donor group. It was shown by Warshel and Papzan [4] that the novel aspect of LBHB is a more covalent character accompanied by a more disperse charge distribution resulting in different energetic especially in response to its environment. It has been proposed earlier [5] that hydrogen bonding and proton transfer reactions can be

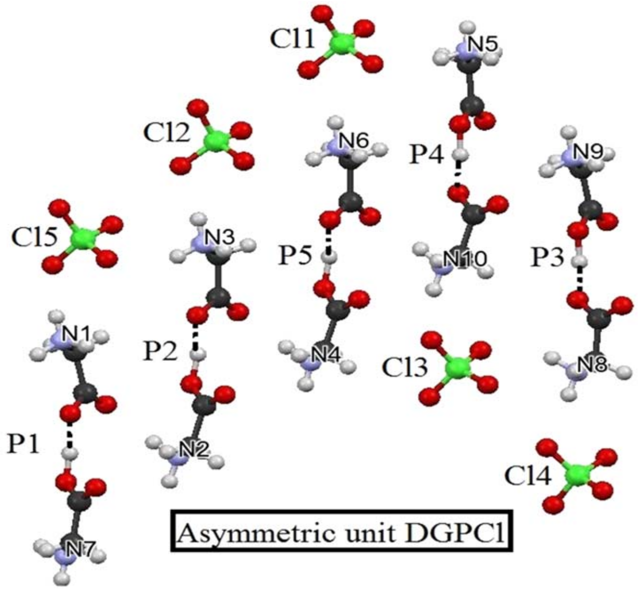

Figure 1. Asymmetric Unit of DGPCl.

described by Empirical Valence Bond models involving valence bond states, according to the three-orbital four electron model for hydrogen bond X–H–Y following three valence bond states are involved in the Hamiltonian

$$\psi_1 = X - H\ Y^{-} \psi_2 = X^{-}H - Y\ \psi_3 = X^{-}H^{+}\ Y^{-}$$

For ordinary hydrogen bonds with negatively charge acceptor the charge is primarily concentrated at the acceptor end (Y) this corresponds primarily to the resonance structure ψ_1 in contrast for LBHB the charge is spread out because of charge transfer effects hence the situations corresponds more towards the resonance structure $\psi_{3.}$

The significance of LBHBs in macromolecular interactions has been highly controversial [6], despite may attempt the existence and potential importance of protein LBHBs remains debatable. One reason for this is that clear experimental evidence of LBHB in macromolecular crystallography is rare since firstly it is proposed to exist in the transition state only which is difficult to crystallize and secondly even the best x-ray structures of macromolecules do not give H atom positions precisely. Hence in order to answer questions like whether or not a distinct class of LBHBs exists and if they do exist under what conditions they are formed and how do they behave differently from OHB one has to fall back to studying small molecular structures proposed to contain LBHBs.

Diglycine perchlorate (DGPCl) is one such small molecular structure that gave us an opportunity to study subtle differences in the nature of short strong hydrogen bonds, the structure contains five unique charge assisted hydrogen bonds [7], each of these hydrogen bonds have the potential to be a LBHB. DGPCl is a crystalline adduct obtained from 2:1 aqueous solution of Glycine and Perchloric [8] acid. Its crystal structure [8] is Triclinic with space group P-1, an asymmetric unit (figure 1) of DGPCl has five strongly hydrogen bonded positively charged glycinium-glycine pairs (P1-P5) and five negatively charged perchlorate ions. Table 1 gives structural details for the five O-H–O hydrogen bonds between the carboxyl (-COOH) and carboxylate ($-COO^{-}$) groups of glycinium-glycine pairs of DGPCl at two different crystal temperatures 293 K and 150 K. Carboxyl-Carboxylate supramolecular motifs [9] are important synthon in bimolecular systems, O-H–O bond between the carboxyl and carboxylate groups has the potential to be a LBHB [6] since the primary requirement for the formation of LBHB [4] namely a close matching of pKa values of the donor and acceptor groups can be easily satisfied in this case.

Computation method

In order to obtain the properties like partial atomic charges, bond orders etc for the atoms and bonds of the glycinium-glycine pair PM6 semi-empirical quantum calculation method [10] as implemented in software MOPAC2016 [11] is used. Experimentally obtained molecular geometry of the glycinium-glycine pair is used in the calculation. Table 2 lists these properties for the atoms and bonds involved in O-H–O H-bonds of DGPCl. Hydrogen bond stabilization energy E_{HB} resulting due to O-H–O bond between Glycinium (Gly^{+}) and Glycine

Table 1. Details of O-H–O hydrogen bond geometries for glycine-glycinum pairs of DGPCl at 293K and 150K, Δ is the difference between O-H and H–O segment lengths its value approaches zero for LBHB.

Pair	O-H (Å)	H—O (Å)	O–O (Å)	Δ (Å)	C–O & C=O (Å) Acceptor	C–O & C=O (Å) Donor
P1(293K)	1.04(2)	1.43(2)	2.466(2)	0.39	1.271(2) & 1.237(2)	1.283(2) & 1.288(2)
P1(150K)	0.99(2)	1.47(2)	2.455(2)	0.48	1.276(2) & 1.236(2)	1.232(2) & 1.230(2)
P2(293K)	1.08(2)	1.39(2)	2.459(2)	0.31	1.260(2) & 1.246(2)	1.288(2) & 1.220(2)
P2(150K)	1.07(2)	1.39(2)	2.452(2)	0.32	1.265(2) & 1.248(2)	1.296(2) & 1.217(2)
P3(293K)	1.12(2)	1.35(2)	2.467(2)	0.23	1.257(2) & 1.246(2)	1.294(2) & 1.218(2)
P3(150K)	1.12(2)	1.35(2)	2.462(2)	0.23	1.264(2) & 1.249(2)	1.299(2) & 1.223(2)
P4(293K)	1.10(2)	1.37(2)	2.466(2)	0.27	1.267(2) & 1.239(2)	1.289(2) & 1.230(2)
P4(150K)	1.03(2)	1.43(2)	2.454(2)	0.40	1.277(2) & 1.238(2)	1.293(2) & 1.233(2)
P5(293K)	1.14(2)	1.33(2)	2.473(2)	0.19	1.258(2) & 1.248(2)	1.299(2) & 1.219(2)
P5(150K)	1.20(2)	1.27(2)	2.468(2)	0.07	1.267(2) & 1.249(2)	1.303(2) & 1.219(2)

Table 2. Bond order and Atomic charges for the atoms involved in O-H–O hydrogen bonds of DGPCl, charge and energy calculation done using MOPAC2016, pKa$_1$ is the pKa value for the donor, pKa$_2$ is the pKa value for the acceptor and ΔpKa is the pKa difference.

pair	Bond order O1-H H–O2 O1—O2	Charge O1 H O2	pKa$_1$ pKa$_2$ ΔpKa	E$_{HB}$ (Kcal mol^{-1})
P1 (293K)	0.676 0.137 0.042,	−0.573 0.394 −0.709	−7.21 −1.22 −5.99	−7.80
P1 (150K)	0.709 0.113 0.038	−0.558 0.383 −0.718	−7.84 −0.81 −7.02	−6.86
P4(293K)	0.630 0.173 0.049	−0.599 0.404 −0.693	−6.04 −1.91 −4.13	−8.37
P4(150K)	0.684 0.133 0.042	−0.565 0.390 −0.714	−7.56 −3.65 −3.91	−7.38
P2(293K)	0.638 0.166 0.049	−0.604 0.403−0.689	−5.84−2.08−3.76	−8.48
P2(150K)	0.644 0.163 0.049	−0.607 0.400 −0.693	−5.69 −1.92 −3.77	−7.94
P3(293K)	0.605 0.193 0.053	−0.627 0.409 −0.682	−4.83 −2.42 −2.40	−9.04
P3(150K)	0.605 0.194 0.054	−0.631 0.409−0.680	−4.63 −2.47 −2.16	−9.39
P5(293K)	0.586 0.209 0.056	−0.641 0.413 −0.672	−4.21 −2.84 −1.37–	−9.89
P5(150K)	0.523 0.266 0.063	−0.672 0.420 −0.654	2.83 −3.65 0.82	−11.89

(Gly) is obtained as following:

$$\mathrm{EHB} = \mathrm{E(Gly + –Gly)} - [\mathrm{E(Gly+)} + \mathrm{E(Gly)}]$$

Here E(Gly^{+}–Gly), E(Gly^{+}) and E(Gly) are the calculated values of total energy for the glycinium-glycine pair, glycinium ion and glycine Zwitter ion respectively.

It can be observed (table 1) that the H atom in all the five O-H–O bonds of DGPCl is placed asymmetrically resulting in unequal proton sharing between the donor and acceptor molecules. It is known that the extent to which a functional group can be protonated or deprotonated by the hydrogen transfer from/to the environment is determined by its pKa. The pKa values are usually determined experimentally by potentiometric, spectrophotometric, chromatographic, electrophoresis, calorimetric. conductometric, and NMR techniques. Need for accurate estimation of pKa using theoretical methods was felt for cases where the pKa measurements of molecules or part of molecules were difficult by experimental means. Recently Haslek *et al* [12] have proposed a protocol to theoretically compute the carboxylic acid pKa using the value of atomic charges on carboxylic group atoms, according to this method following equation can be used to get a theoretical estimate of carboxylic acid pKa:

$$\mathrm{pKa} = \mathrm{a.Q} + \mathrm{b}(\text{here: } a = -43.968\ \&\ \mathrm{b} = -32.411)$$

Q here is the maximum atomic charge on the carboxylic oxygen. As the donor as well as the acceptor groups for the O–H—O bonds between the glycinium-glycine pairs of DGPCl are partially ionized Carboxylic groups we have use the above mentioned method to computed their pKa values (table 2), the atomic charges listed in table 2 are used in the calculation.

Discussions

When room temperature (293K) structure of DGPCl is looked into closely following subtle structural features are noticed (table 1): variation in the donor–acceptor O–O distance for all the O-H–O bonds is small (within 0.014Å), H-bond of glycinium-glycine pair labelled P2 has the shortest O–O separation (2.459Å), where as H-bond of P5 has the longest (2.473Å) O–O separation, the H-bonds of three other pairs P1(2.466Å), P4(2.466Å) and P3(2.467Å) have very similar O–O separations, however the O-H covalent bond length for all the pairs varies much more significantly (within 0.10 Å): $P1(1.04\text{Å}) < P2(1.08\text{Å}) < P4(1.10\text{Å}) < P3(1.12\text{Å}) < P5(1.14\text{Å})$. When the hydrogen bond geometries for the five O-H–O bonds at 293K temperature are compared to those at 150 K (table 1), it is observed that all the O–O distances reduce due to thermal contraction, in addition it is observed that there is a reduction in the O-H covalent bond lengths of P4 (-0.07Å), P1(-0.05Å) and P2 (-0.01Å), nearly no change in the O-H covalent bond length of P3 (-0.00Å) but there is an increase in the O-H covalent bond length of P5 ($+0.06$Å). If thermal contraction of the unit cell is equated to applying pressure then the above observation indicates that application of pressure strengthens O-H covalent bonds of P1, P2 and P4, has very small effect on O-H covalent bond of P3 but it has an opposite effect on the O-H covalent bond of P5 resulting in its weakening leading to near symmetrisation of its O-H–O hydrogen bond at lower temperature. This is a clear indication that the nature of O-H–O bonds of P1, P2 and P4 is different from that of P5 and hydrogen bond of P3 has intermediate nature.

Looking at the results of E_{HB} calculation (table 2) it is concluded that the O-H–O hydrogen bonds of DGPCl are of varying strength, the hydrogen bond strength for the five pairs varies as following: $P1 < P4 < P2 < P3 < P5$. It is important to note that contrary to common expectation that stronger hydrogen bonds have smaller O–O separation, in case of DGPCl P5 that has the longest O–O separation has the strongest hydrogen bond moreover it is observed that P1, P4 and P3 have nearly identical O–O separation but their hydrogen bond strength varies significantly. These observations indicate that there are factors other than the donor–acceptor separation that can affect the hydrogen bond strength; one such factor is diffusivity of acceptor electron density; an earlier systematic study of O-H–O hydrogen bonds with different acceptor groups had shown that acceptors with diffusive electron density made stronger hydrogen bonds [12]. Diffusivity of carboxylate group electron density depends directly on its resonance structure, for DGPCl H-bonds it is observed that the resonant nature of acceptor carboxylate group varies (table 2) as following: $P1 < P4 < P2 < P3 < P5$ which is same as the variation of hydrogen bond strength for the five pairs. This can be taken as an indication that acceptor group electron density might play a role in determining the strength of the O-H–O hydrogen bonds of DGPCl, i.e. higher resonant nature of the acceptor group might lead to stronger H-bond.

Formation of hydrogen bond is accompanied by charge redistributions [13, 14], dipolar field created by the donor and acceptor fragments is responsible for most of the intramolecular charge redistribution, in addition to this polarization driven charge redistribution a small amount of charge is transferred locally from acceptor to the donor upon hydrogen bond formation, this gives an estimate of the covalent contribution to the hydrogen bond. The positive charge of bridging H atom increases with hydrogen bond formation, in addition there is a electron density flows from the proton acceptor molecule to the donor, causing a greater negative charge on the donor atom and more positive charge on the acceptor atom. It is observed that for DGPCl the partial charge on the donor oxygen atoms varies as $P1 < P4 < P2 < P3 < P5$, this leads us to conclude that the covalent contribution to these hydrogen bonds vary as $P1 < P4 < P2 < P3 < P5$. This conclusion is also supported by the calculated values of O–H bond order reported in table 2. Earlier *Ab initio* quantum calculations [15] demonstrated that the delocalization index derived from Quantum Chemical Topology (QCT) serves as bond order, hence for a given bond the value of bond order gives a measure of electron sharing. Looking at the bond order values of O–H bonds (table 2) it is concluded that the electron sharing between the H atom and accepter O varies as $P1 < P4 < P2 < P3 < P5$.

A recent study [16] on pairwise interaction between atoms and its dependence on range of possible distances between the atoms demonstrated that the nature of interaction between H and O atom changes continuously with the distance between them. The authors of this study showed that as the distance between H and O atoms changed the nature of interatomic interaction gradually changed from primarily covalent in the range 0.58–1.36Å to primarily electrostatic in the range 1.36–2.14Å to primarily dispersive in the range 2.14–2.92Å, the authors predicted the occurrence of chained interactions of varying nature and strength between H and O atoms. Based on these results we can classify the O–H interactions between the H atoms and acceptor O atoms of the H-bonds of DGPCl as following: for P1, P2 and P4 pairs H–O interactions is primarily electrostatic in nature, for P5 pair the H–O interactions is primarily covalent in nature and H–O interaction for P3 pair lies in the transition region between the electrostatic and covalent nature. As stated earlier one of the main distinguishing characteristic between the OHB and LBHB is the degree of covalency of the H–O interactions hence we conclude that LBHB nature of the five O-H–O hydrogen bonds of DGPCl varies as $P1 < P4 < P2 < P3 < P5$.

In order to further support our conclusion we tried estimating the pKa difference (ΔPka) between the donor and acceptor groups since the existence of LBHB [4] is possible only for cases where $\Delta\text{pKa} \sim 0$. Table 2 lists the calculated pKa values for the donor and acceptor groups of H-bonds of DGPCl along with the pKa differences at two temperature (293 K & 150 K). Using the pKa slide rule for hydrogen bonds [17] which states that strong hydrogen bonds that have the potential to be a LBHB have ΔPka in the range -3 to 3, we conclude the hydrogen bonds in pair P5 and P3 are the ones that can belong to LBHB where as the H-bonds of remaining pairs are strong OHBs.

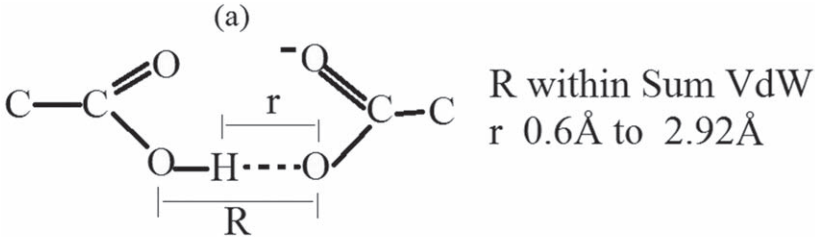

Figure 2. Molecular Fragment used to extract structures from CSD having O-H–O H-bonds between Carboxyl-Carboxylate groups.

In order to test the above conclusion regarding the nature of the O-H–O bonds of DGPCl we looked into the changes brought about in these H-bonds by changing the environment i.e. we analysed the changes brought about in H-bond geometry and energetic by varying the crystal temperature. As stated earlier the O-H covalent bond lengths for H-bonds of pairs P1, P2 and P4 that have been classified as strong OHB decrease with decrease in temperature, in contrast the O-H covalent bond length for H-bond of pair P5 that has been classified as LBHB increases with decrease in temperature making this H-bond nearly symmetric at 150 K, finally O-H covalent bond length for H-bond of pair P3 that lies in the transition region shows no change. The above observation clearly shows the nature of LBHB is different from OHB and there is a continuous variation in the H-bond nature from OHB to LBHB as the covalent contribution to the H-bond interaction increases.

O-H–O hydrogen bond interaction can be viewed as an interaction between three particles, in general three potentials are required to describe such an interaction [18–20], first describing the O-H covalent bonded interaction, second describing the O–H hydrogen bridge and third describing the direct O–O interaction. For understanding the nature of O-H–O bonds it is usually [20] segmented into a shorter H-O covalent bond and a longer O–H nonbond/hydrogen bridge, O-H and H–O segments act like a pair of coupled oscillators. Usually for calculation purpose potentials describing the O-H covalent bond and the O–H nonbond are taken to have similar form [19]. For ordinary hydrogen bonds shorter O-H segment has covalent nature and the longer O–H segment has electrostatic or dispersive nature, this difference is accounted for in calculation by using different parameter values [20] in potentials describing the two segments. Pressure response for this hydrogen bonded system was shown [20] to be such that O-H bond becomes shorter with pressure and O–H nonbond becomes longer, hydrogen atom remains bonded to original donor atom and there is no pressure induced symmetrisation of such a hydrogen bond. It was demonstrated by Holzapfel [18] that in special cases where both O-H segment and O–H segment posses partial covalent nature as in the case of LBHB, same potentials parameters have to be used to describe the two segments of the hydrogen bond. Pressure response for such a system is very different from that seen in ordinary hydrogen bond described previously, it was shown [18] that under pressure O-H bond of this system lengthen and O–H nonbond shortens i.e. the O-H–O hydrogen bond becomes more and more symmetric with pressure. Using these results we can explain the behaviour of hydrogen bonds of DGPCl as following : O-H–O hydrogen bonds of pairs P1, P2and P4 belong to the category of OHB hence show no symmetrisation due to thermal pressure, whereas hydrogen bond of Pair P5 belongs to the LBHB, application of thermal pressure leads to symmetrisation of this O-H–O hydrogen bond. The O-H–O hydrogen bond of pairs P3 lie in-between these two categories of hydrogen bonds. These observations clearly show that LBHB is a distinct class of strong hydrogen bonds that behaves differently from strong OHBs.

In order to find how common the LBHBs are and whether the conclusions obtained from analysing the nature of O-H–O bonds of DGPCl can be generalized, Cambridge structural database (CSD version 5.43 November 2021) is data mined for structures containing Carboxyl-Carboxylate supramolecular motif (figure 2(a)). We have searched the CSD using the DRAW option available in ConQuest program [21], only organic crystal structures obtained from single crystal diffraction technique with R-factors less than 5% were considered. Table 3 lists the complete details of the search. Based on the study by Labato *et al* [14] we have classified O-H–O H-bonds into three categories namely covalent HB having H–O distance within the range 0.58–1.36Å, electrostatic HB having H–O distance within the range 1.36–2.14Å and dispersive HB having H–O distance within the range 2.14–2.92Å. Nearly 92% of charge assisted hydrogen bonds between Carboxyl-Carboxylate belong to the category of electrostatic HB, less than 1% belong to the category of dispersive HB and finally approximately 7% belong to the category of covalent HB, these H-bonds show LBHB characteristics as is evident from very similar O-H and H–O segment lengths of these bonds (difference between the lengths of O-H and H–O segments is less than 0.23Å for this category). Significantly lower value of correlation coefficient between the donor–acceptor O–O distance and the O–H hydrogen bridge length in covalent HB category is an indication that strength of H-bonds in this category depends not just on the donor–acceptor distance but other factors like the nature of acceptor electron density also play a part, these factors become less important for

Table 3. Details of CSD Search.

O–H Range(Å)	Total No. HBs (Å)	L(H–O)-L(O-H) (Å) maximum value	⟨H–O⟩ (Å)	⟨O–O⟩ (Å)	⟨OHO⟩ (°)	Correlation (O–O) & (O–H)
Covalent HB(0.58–1.36)	38	0.23	1.292	2.460	172.3	0.41
electrostatic HB(1.36–2.14)	464	1.26	1.640	2.538	169.8	0.62
dispersive HB(2.14–2.92)	4	1.77	2.451	2.982	117.9	0.99

H-bonds belonging to electrostatic and dispersive category. It is important to state that nearly all the O-H–O hydrogen bonds belonging to the covalent HB category are between conjugate acid–base pairs, combining this general observation with the particular observations made in case of O-H–O bonds of DGPCl we can state the H-bond between conjugate acid–base pairs can be an LBHB only under certain condition and that condition is near perfect pKa matching of donor and acceptor groups as in the case of O-H–O bond of pair P5 of DGPCl, a small redistribution of electron density of either the donor as acceptor group can disturb this condition as is seen in case of O-H–O bonds of pairs P1, P2, and P3 of DGPCl resulting in changing the nature of H-bond from LBHB to strong OHB . These statistics show LBHBs occur rarely in nature but where ever they occur they play distinctly different role as compared to an OHB.

It is interesting to compare the nature [22] of LBHBs to the symmetric double well hydrogen bonds (SDWHB) found in crystals like Triglycine sulphate [23] (TGS) and Potassium Dihydrogen Phosphate [24] (KDP). Although the energy contours for both these types of hydrogen bonds has symmetric double well form the barrier height for SDWHB is high enough to ensure that proton is covalently bonded only to one of the atoms (donor/acceptor), hence SDWHB are ordinary hydrogen bonds with two symmetry equivalent H positions. Since the difference between the lengths of O-H and H–O segments of O-H–O bonds is larger for SDWHB (L(H–O)-L(O-H) $>$ 0.35Å for KDP & TGS) as compared to that seen in LBHBs (L(H–O)-L(O-H $<$ 0.23Å) what one observes in case of SDWHBs is dynamic disorder of protons due to barrier hopping and not proton delocalization as in case of LBHB. Proton conductions studies [25] have demonstrated that in order to have large proton conductivity presence of SDWHB is required within the material; in contrast presence of LBHB can result in lower conductivity due to partial proton transfer.

The above discussion shows that we can have strong ordinary hydrogen bonds with energy landscape symmetric or asymmetric (SDWHB & ADWHB respectively) depending on the whether the pKa difference between the donor and acceptor is close to zero or non-zero, but in either case the H-atom is primarily covalent bonded to one atom and interacts electrostatically with the other (figures 3(a) and (b)). OHBs found in DGPCl pairs P1, P2 & P4 belong to the category ADWHB where as those found in KDP and TGS crystals belong to the category SDWHB. In Contrast the energy landscape for LBHB is such that H-atom is partially covalently bonded to both donor and acceptor atoms as is seen for the case of H-bond of pair P5.

In order to demonstrate the above mentioned differences between SDWHB, ADWHB and LBHB we have generated the H-bond potential energy contours for the three different types of H-bonds using Diabatic state model [26–28] for hydrogen bonds (detailed expression for potential energy used in calculation are given in appendix), for the sake of comparison O–O distance for all the three cases is taken as 2.48Å (figure 3), the difference in shape of the potential is obtained by varying the potential parameters V_0 that takes into account the asymmetry between the donor and acceptor atoms and Δ_1 which is proportion to the overlap of lone pair orbital of acceptor atom with the orbital on the donor. Ground state energy (E_0) as well as ground state wavefuction (Ψ_0) for the calculated potentials is obtained using the program FINDIF [29]. It is observed that for ordinary hydrogen bonds ADWHB & SDWHB the potential barrier height is significantly higher than the ground state energy (figures 3(a) and (b)), the H-atom wavefunction is largely confined to one potential well, for the symmetric case H-atom hops between the two potential wells resulting in two maxima in the wavefunction, H-atom hopping is purely a classical phenomenon dependent on the sample temperature and H-bond hopping can be stopped by lowering the temperature as seen in case of KDP crystals. However in case of LBHB (figure 3(c)) potential barrier height is of the order of the ground state energy, H-atom wave function is spread over both the wells resulting in H-atom making partial covalent bond with both donor as well as acceptor atoms, this phenomenon will be temperature independent as long as the donor–acceptor distance remains unchanged with temperature.

Conclusion

We started off looking for concrete experimental evidence to answer questions like whether or not a distinct class of hydrogen bonds namely LBHBs exists and if it does exist under what conditions these H-bonds are formed

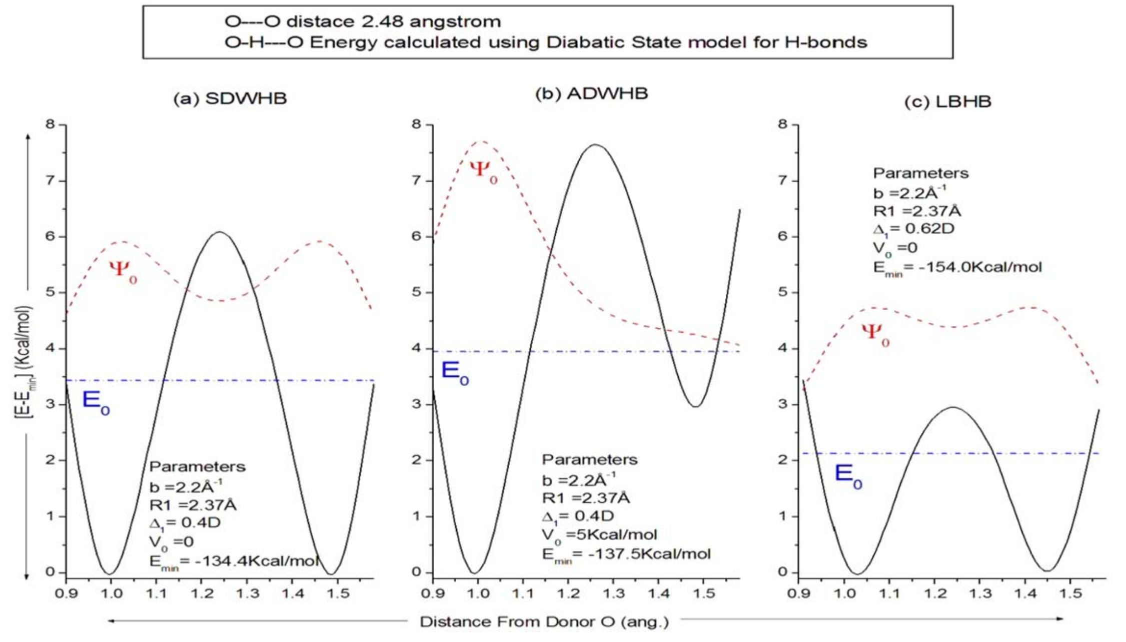

Figure 3. Hydrogen bond potentials for SDWHB, ADWHB and LBHB calculated using the Diabatic state model for hydrogen bonds.

and how do they behave differently from ordinary hydrogen bonds. Diglycine Perchlorate crystal structure gave us a unique opportunity to make a comparative study of the intrinsic nature of strong charge assisted hydrogen bonds; the crystal contains five hydrogen bonded glycinium-glycine pairs P1-P5, each of these pairs had slightly different charge distributions resulting in observable variations in their hydrogen bonds. A minute analysis of these variations in hydrogen bond geometries and charge distributions at two different crystal temperatures (293 K & 150 K) led us to the following conclusions regarding the nature of these hydrogen bonds.

- A close look at DGPCl crystal structure at 293K revealed that the O–O distances for all the O-H–O bonds are similar (varying within 0.014Å) but there is a much larger difference in their O-H covalent distances (varying within 0.10Å). This can be taken as an indication of varying strength of these short strong H-bonds since increase in the O-H covalent bond length is the most important indicator of H-bond strength. Energy calculation showed that the strength of O-H–O bonds between the five glycinium-glycine pairs of DGPCl varies as P1 < P4 < P2 < P3 < P5. It is observed that contrary to common expectation that stronger hydrogen bonds have smaller O–O separation, in case of DGPCl P5 that has the strongest hydrogen bond has the longest O–O separation. This indicates that there are subtle factors that affect the strength of short strong hydrogen bonds having similar donor–acceptor distances. These can be factors like differences in electrostatic and covalent contributions to total energy of H-bond resulting from small differences in acceptor electron densities.

- Looking at the calculated charges on donor and acceptor O atoms of O-H–O bonds of DGPCl it is concluded that the net flow of electron density from the acceptor glycine to the donor glycinum of glycinium-glycine pairs varies as following P1 < P4 < P2 < P3 < P5, this is taken as an indication of how the covalent contribution to O-H–O bonds vary. It is already known that the main distinguishing characteristic between the OHB and LBHB is the degree of covalency of the H–O interactions, hence the above stated observation leads to the conclusion that LBHB nature of the five O-H–O bonds of DGPCl varies as P1 < P4 < P2 < P3 < P5.

- Calculated pKa difference (ΔpKa) between the donor and acceptor groups obtained using the recently proposed protocol by Haslek *et al* [14] further supported the above conclusion. Using the pKa slide rule for hydrogen bonds [15] which states that strong hydrogen bonds that have the potential to be a LBHB should have ΔpKa in the range −3 to 3, we conclude that the hydrogen bonds in pair P5 and P3 are the ones that can belong to LBHB where as the hydrogen bonds in pair P1, P2 and P4 are strong OHBs.

- Since OHB and LBHB are expected to respond differently to changing environment, the above stated conclusion can be tested by studying the behaviour of O-H–O bonds of DGPCl under different environments like different crystal temperatures. It is observed that the O-H covalent bond lengths for O-H–O H-bonds of pairs P1, P2 and P4, that have been classified as strong OHB, decrease with decrease in temperature, in contrast the O-H covalent bond length for O-H–O H-bond of pair P5, that has been classified as LBHB, increases with decrease in temperature making the H-bond nearly symmetric, finally O-H covalent bond length for O-H–O H-bond of pair P3 that lies in the transition region shows no change. This clearly shows that compared to OHBs the LBHBs respond differently to environment changes.

- Cambridge structural database analysis of general properties of O-H–O bonds between Carboxyl-Carboxylate groups in organic small molecules shows that these H-bonds are mainly electrostatic in nature and only small fraction of these H-bonds that are predominantly covalent in nature belong to the LBHB class.

Based on the above stated conclusions regarding the nature of LBHBs we are now in a much better position to answer the questions we started with, this study gives an experimental evidence of the existence of LBHBs and demonstrates that the behaviour of LBHBs is very different from that of strong OBHs. Unlike OHBs that are very commonly observed in biomolecules LBHBs are rare and wherever present they are expected to fulfil specialized roles, this fact was recently demonstrated by a study by Shaobo Dai *et al* [30] in which they observed a fluctuating LBHB acting as a switching element in cooperativity pathways of multimeric enzymes.

Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

Appendix: Diabatic state model for H-bonding

According to the diabatic model the O-H···O hydrogen bond can be represented by two interacting diabatic states $|\text{O-H}\cdots\text{O}\rangle$ and $|\text{O}\cdots\text{H-O}\rangle$ .The effective Hamiltonian describing the two interacting diabatic states has the form

$$\mathrm{H} = \begin{pmatrix} V(r) & \Delta(R) \\ \Delta(R) & V(R - r) + V0 \end{pmatrix}$$

Where V(r) = D[$e^{-2a(r-r0)} - 2e^{-a(r-r0)}$], is Morse potential for O-H bond with a depth (D) of 120 kcal mol^{-1}, exponential parameter a = 2.2Å^{-1} corresponding to O-H stretch harmonic frequency of 3600 cm^{-1}. r and R are the O-H and O–O distances respectively and r0 is the equilibrium free O-H distance of 0.96Å.V_0 is the vertical off set to take into account the asymmetry of the O-H···O hydrogen bond. The coupling between the diabats $|\text{O-H}\cdots\text{O}\rangle$ and $|\text{O}\cdots\text{H-O}\rangle$ is given by Δ(R) defined as

$$\Delta(\mathrm{R}) = \Delta1 \exp\left[-\mathrm{b}(\mathrm{R} - \mathrm{R1})\right]$$

This model has essentially two free parameters b and Δ_1.

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