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Effect of alkyl substitution on H-bond strength of substituted amide-alcohol complexes

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Abstract The effect of alkyl substitution (CH_3 , C_2H_5 , $n\text{-C}_3\text{H}_7$, $i\text{-C}_3\text{H}_7$, and $t\text{-C}_4\text{H}_9$) on the hydrogen bond strengths (H-bond) of substituted amide-alcohol complexes has been systematically explored. B3LYP/aug-cc-pVDZ method was applied to a total of 215 alkyl substituted amide-alcohol complexes to delineate the effect of substitution on the H-bond strength; formamide-water complex is taken as reference point. Complexes are classified into five types depending on the hydrogen donor, acceptor and the site of alkyl substitution (Type-IA, Type-IIA, Type-IB, Type-IIB and Type-III). The strength of H-bond was correlated with geometrical parameters such as proton-acceptor ($\text{H}\cdots\text{Y}$) distance, the length of proton donating bond (X-H). In all the complexes N-H and O-H stretching frequencies are red-shifted. The effect of alkyl substitution on N-H and O-H stretching frequencies were analyzed. Topological parameters like electron density at $\text{H}\cdots\text{Y}$ and X-H bond critical points as derived from atom in molecules (AIM) theory was also evaluated. When C=O group is participating in H-bond, the strength of H-bond decreases with increasing size of alcohols except for methanol (Type-IA, Type-III and Type-IB complexes). But it increases with increasing size of alkyl groups on amide and decreases with bulky groups. In the case of N-H group as H-bond donor, the strength of H-bond increases with increasing size of alcohols (Type-IIA and Type-IIB complexes) whereas

decreases with increasing size of alkyl groups on amide. Type-IA, IIA, IB and IIB complexes exhibit good correlations among IE, H-bond distance and electron density at bcp. In Type-III complexes, average H-bond distance and sum of electron densities shows better correlation with IEs than the corresponding individuals. The correlation of IE less with electron density at RCP compared to sum of electron densities.

Keywords Amide linkage · Hydrogen bonding · DFT calculations · Substituent effects

Introduction

Hydrogen bond (H-bond) plays a significant role in various chemical and biological systems including stabilizing biomolecular structures, modulating specificity and speed of enzymatic reactions and constructing supramolecular structures [1–6]. H-bond is mainly observed in biomolecules generally through involvement of amide group ($-\text{CONH}-$) especially in proteins. The dual ability of amide group to act as both H-bond donor and acceptor makes the linkage versatile in molecular assembly and recognition [7]. Among peptide bonds in proteins, H-bond is the key driving forces for forming secondary structures namely α -helix and β -sheets. The linkage also plays an important role in the pharmacophores of the anti-bacterial agents such as penicillin and carbacephem and has been utilized in designing enzyme inhibitors [8, 9]. H-bond is usually represented in the form of $\text{R-X-H}\cdots\text{Y-R}^1$, where X and Y are electronegative elements. While studying the structures and properties of H-bonds, the attention is on the atoms (X, Y, and H) participating directly in the formation of H-bonds. The properties and strengths of H-bonds are

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determined mainly by the properties of these atoms, but the alkyl groups adjoining to these atoms also exert a substituent effect which significantly alters the properties and functions of H-bonds [10–23]. Ramos et al. [22] studied the strength of the $\pi\cdots\text{HF}$ H-bond between acetylene and HF, which enhanced with increasing methyl substitution in C_2H_2 . The effect of methyl substitution on H-bond strength was studied for pyridine-water system, where the complex gets stabilized with increasing the number of methyl groups in methyl substituted pyridine [23]. Li et al. [24, 25] studied the role of methyl groups in conventional ($\text{O}\cdots\text{H}-\text{O}$) and unconventional ($\text{C}-\text{H}\cdots\text{O}$) H-bonds. They studied the role of methyl groups in the formation of $\text{O}\cdots\text{H}-\text{O}$ H-bond between dimethyl sulfoxide (DMSO) and methanol. The methyl group in DMSO is electron donating, whereas that in methanol is electron withdrawing; both contribute to the stabilization of H-bond [24]. The function of methyl groups in the strength of the $\text{C}-\text{H}\cdots\text{O}$ H-bond was studied with $\text{XC}\equiv\text{C}-\text{H}$ ($\text{X}=\text{H}$, CH_3 , F) as H-bond donor and YOH ($\text{Y}=\text{H}$, CH_3 , Cl) as H-bond acceptor. Methyl substitution of the proton acceptor strengthens the $\text{C}-\text{H}\cdots\text{O}$ bond, whereas that of the proton donor weakens the $\text{C}-\text{H}\cdots\text{O}$ bond. The methyl group of the proton acceptor is electron withdrawing and that of the proton donor is electron-donating in the formation of $\text{C}-\text{H}\cdots\text{O}$ bond [25]. Formamide complexes such as formamide-water, formamide-methanol and formamide-formamide complexes can serve as model systems for protein-water and protein-solvent interactions, numerous experimental and theoretical studies have been reported [26–41].

In this work, we present quantum chemical studies on H-bond strengths of $\text{C}=\text{O}$ and $\text{N}-\text{H}$ groups with increasing the size of alkyl groups on amide and alcohols. The results in this work are compared with available experimental and theoretical results. Furthermore, according to the classical drug design paradigm, the effect of a drug in the human body is a consequence of the molecular recognition between drug and biological target. The pharmacological activity of a drug is ultimately determined by the interactions between the drug and its target. H-bond is one of the major forces for the interactions. In the drug optimization process, some of the underlying causes of the structure-activity relationships could be traced to a modulation of the H-bond interactions of the drug with the biological partner. Because the amide linkage is an important building block in drugs, the variations of the H-bond strength may be utilized in the drug design or refinement for improving the specificity and affinity, which is, in part, the motivation of the present study.

One contentious issue to estimate the strength of an individual noncovalent interaction is lack of quantitative measures, which are exclusively connected with the

strength of the hydrogen bond. For example, the interaction energy of the hydrogen bonded complex may also get strongly influenced by through space and through bond interactions, besides other long range stereoelectronic effects. Thus, the current study is aimed to gauge the efficacy of bond length and topological measures which exclusively correspond to H-bond and find out how they correlate with the interaction energy.

This paper is organized in the following way. Section 2 describes computational methods; section 3 describes nomenclature of complexes used in the present study; section 4 includes results and discussion, in this 4.1 enlightens about Type-IA, Type-IIA (4.2), Type-III (4.3), Type-IB (4.4) and Type-IIB (4.5) complexes. Finally section 5 gives the concluding remarks of this study.

Computational methods

A comparative study on formamide-water complexes reveal that B3LYP/aug-cc-pVDZ method is appropriate for formamide-water complexes [41]. All structures are optimized without imposing any constraints at B3LYP level with aug-cc-pVDZ basis set using Gaussian 03 set codes [42]. The frequency analysis characterizes that all conformations considered as minima on the potential energy surface. The H-bond energies are calculated using Eq. 1. To take into account the effect of the basis set superposition error (BSSE), the counterpoise method was used [43].

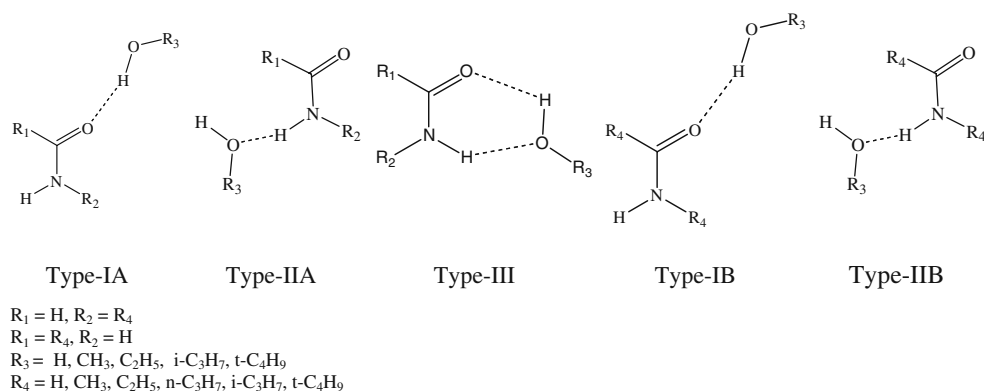
$$\Delta E_{\text{H-bond}} = E_{\text{complex}} - M_{\text{monomers}} \quad (1)$$

The H-bond complexes considered in this study are given in Scheme 1 and classified into five types. The strength of H-bond or interaction energy (IE) was correlated with geometrical and topological parameters such as proton-acceptor ($\text{H}\cdots\text{Y}$) distance, the length of proton donating bond ($\text{X}-\text{H}$) and electron density at $\text{H}\cdots\text{Y}$ bond critical point. The topological analysis was done using AIM2000 program [44, 45]. The input electron densities were obtained with the Gaussian 03 program at B3LYP/aug-cc-pVDZ level of theory. In addition to geometrical and topological parameters, harmonic vibrational frequencies are also calculated for $\text{H}-\text{O}$ and $\text{N}-\text{H}$ bonds in complex form and monomer molecules to correlate with the strength of IE. The frequency shift ($\Delta\omega$) and intensity change (ΔI) is approximated by Eq. 2 and Eq. 3.

$$\text{Frequency shift}(\Delta\omega) = \omega_{\text{monomer}} - \omega_{\text{complex}} \quad (2)$$

$$\text{Change in Intensity}(\Delta I) = I_{\text{complex}} - I_{\text{monomer}} \quad (3)$$

where $\Delta\omega$ - change in frequency, ΔI - change in intensity, ω_{monomers} , ω_{complex} are the frequencies of monomer and

Scheme 1 The complexes considered in the present study

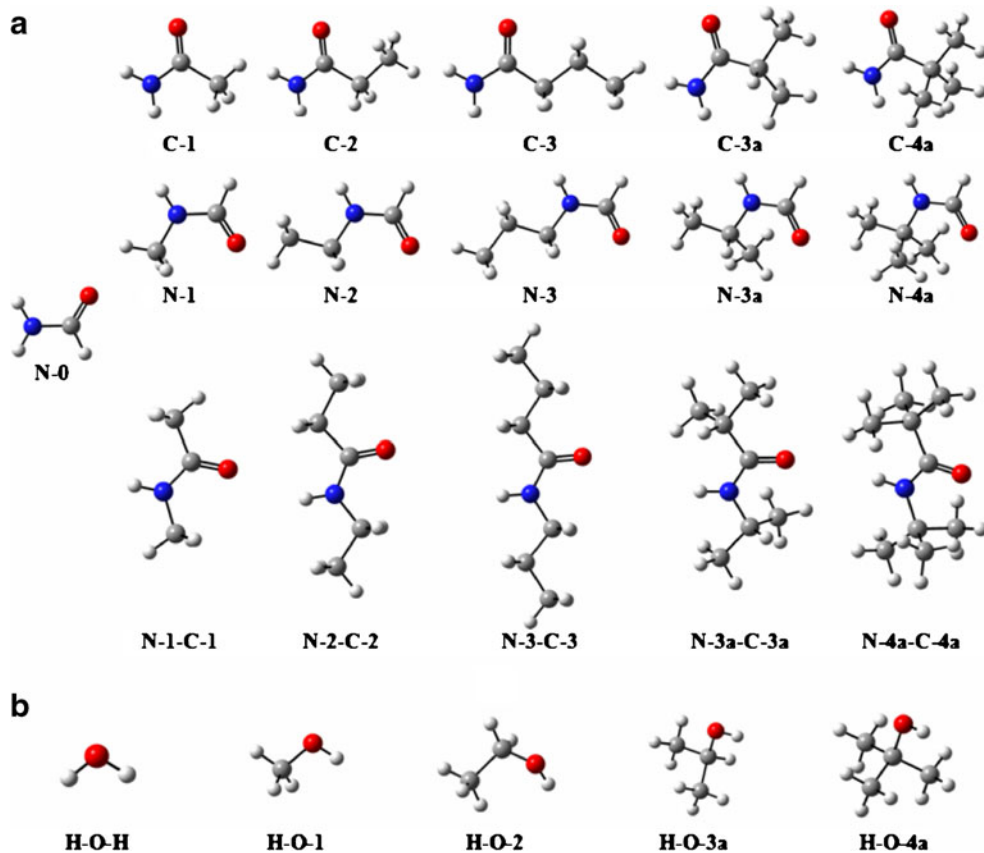
complexes respectively, I_{complex} , I_{monomer} are the intensity of complex and monomers respectively.

Nomenclature

Formamide is represented as **N-0**. In formamide if methyl group (CH_3) is substituted at “C” atom the compound is termed as “**C-1**”, and if it is substituted at “N” atom, termed as “**N-1**”. In the same way ethyl, n-propyl, i-propyl and t-butyl groups substituted at “C” atom of formamide is termed as **C-2**, **C-3**, **C-3a**, **C-4a** and at “N” atom is termed as **N-2**, **N-3**, **N-3a** and **N-4a**

respectively. In the similar manner, alkyl groups substituted at both places (“C” and “N” atoms) of formamide are termed as **N-1-C-1**, **N-2-C-2**, **N-3-C-3**, **N-3a-C-3a**, and **N-4a-C-4a** for methyl, ethyl, n-propyl, i-propyl and t-butyl groups respectively (Fig. 1a). To follow similar nomenclature methyl, ethyl, i-propyl and t-butyl alcohols are termed as **H-O-1**, **H-O-2**, **H-O-3a** and **H-O-4a** respectively (Fig. 1b).

Complexes are classified into five types depending on the hydrogen bond donor, acceptor and the site of alkyl substitution. In formamide if alkyl groups are substituted on either “C” or “N” atom and $\text{C}=\text{O}$ group is participating in hydrogen bond, classified as Type-IA complexes. In

Fig. 1 Nomenclature of compounds, according to alkyl groups attached to (a) formamide (b) water

Type-IIA complexes N–H group participates in hydrogen bonding whereas in Type-III complexes both C=O and N–H groups are involved in hydrogen bonding. Similarly if alkyl groups are substituted on both “C” and “N” atoms of formamide and C=O group is participating in hydrogen bonding classified as Type-IB complexes whereas in Type-IIB complexes N–H group participates in hydrogen bonding (Scheme 1).

Results and discussion

This section is divided into five parts according to Scheme 1 (Type-IA (4.1), Type-IIA (4.2), Type-III (4.3), Type-IB (4.4) and Type-IIB (4.5)) and each part is divided into four sub-parts according to binding energy, geometrical parameters, topological parameters and vibrational frequencies.

Type-IA complexes

Binding energies

In this type of complexes the strongest H-bond is present in **C-3**⋯**H-O-1** complex and the weakest in **N-0**⋯**H-O-3a**, and their corresponding energies are -28.71 and -21.67 kJ mol $^{-1}$ respectively (All this information is available in the supporting information). When considering **H-O-H** as H-bond donor, the strongest energy complex is observed for **C-3** and the weakest for **N-4a** complex while the remaining complexes follows the order as **C-3**>**C-2**>**N-3a**>**C-1**>**C-4a**>**C-3a**>**N-1**>**N-2**~**N-3**>**N-0**>**N-4a**. Urban et al. [46] reported H-bond energy of formamide-water complex at MP2/6-311++G(2d,2p) level as -25.06 kJ mol $^{-1}$ and in the

present study IE is -24.93 kJ mol $^{-1}$. This observation reflects the adequacy of B3LYP/aug-cc-pVDZ method to correctly predict the IEs. Li et al. reported the role of methyl group in conventional and unconventional H-bonds [24, 25]. Methyl groups substituted at “C” or “N” atom of amide have higher IE as compared to formamide-water complex and IEs are -27.54 and -26.33 kJ mol $^{-1}$ for **C-1** and **N-1** complexes respectively. Due to the methyl group substitution the IE increases by 1.5 – 3.0 kJ mol $^{-1}$. The introduction of ethyl leads to a marginal increase (0.2 – 0.5 kJ mol $^{-1}$) in the IE. In **H-O-H** series of complexes, n-propyl substituted complexes such as **C-3** and **N-3** form the strongest H-bonds when compared to the alkyl groups substitution on similar atoms and have stabilization energy higher by 2 – 4 kJ mol $^{-1}$ when compared to formamide-water complex. Further increase the size of alkyl groups (i-C $_3$ H $_7$, t-C $_4$ H $_9$) decrease the strength of H-bond due to steric hindrance. As in **H-O-H** series, similar trend was observed for **H-O-1** and **H-O-2** series except for **N-3a**, **N-4a** complexes, **N-3a** has higher energy as compared to **N-2** and **N-3** complexes whereas **N-4a** has lower energy. In **H-O-1** and **H-O-2** series, strongest IE complex were observed for **C-3** and weakest for **N-0** complexes. Fu et al. [38–57] reported the H-bond strength of formamide-methanol complex at MP2/6-31 G(d,p) level as -25.3 kJ mol $^{-1}$ whereas in the present study IE is -24.90 kJ mol $^{-1}$ again reflecting the adequacy of the chosen method. In all series, the H-bond strength decreases with increasing the size of alkyl group on alcohols except methanol (Fig. 2a). In **H-O-3a** and **H-O-4a** series follows similar trend as observed in **H-O-1** and **H-O-2** series except **N-4a** complexes. Alkyl group substituted at “C” atom of amide has more IE than that of the “N” atom of amide. The strength of IE is correlated with geometrical (4.1.2),

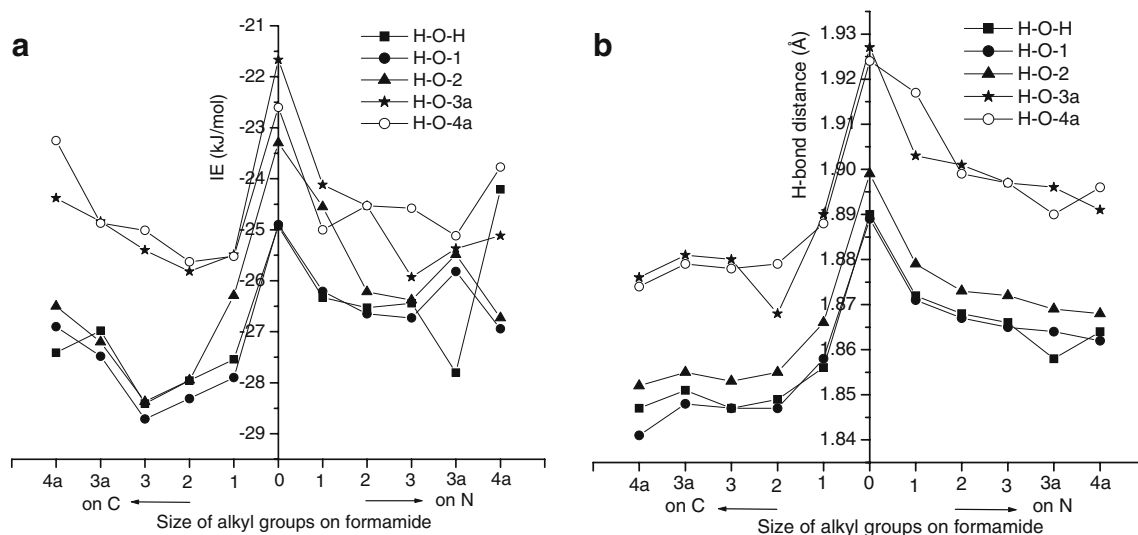


Fig. 2 Variation of (a) IEs (b) H-bond distance with size of alkyl groups in Type-IA complexes

topological (4.1.3) parameters as well as with frequencies (4.1.4), discussed in the following sections.

Geometrical parameters

Figure 2b reflects the variation of H-bond distance of the complexes as a function of the size of alkyl groups. In **H-O-H** series, complex (**C-3**) with the longest O–H distance (0.979 Å) corresponds to the strongest IE ($-28.41 \text{ kJ mol}^{-1}$) and complex (**N-4a**) with smallest O–H distance (0.974 Å) corresponds to the weakest IE ($-24.21 \text{ kJ mol}^{-1}$). Increase in IE with methyl substitution at “C” and “N” atom of amide correlated with increase in O–H bond distances. The relative distances (O–H) of **C-1** and **N-1** complexes with **N-0** complexes are 0.002 and 0.001 Å respectively. The decrease in strength of **N-4a** complex can be attributed by decrease in O–H bond distance by 0.002 Å as compared to the **N-0** complex. Allinger et al. reported H-bond distance and angles of formamide-water complex as 1.907 Å and 156.1° respectively at MP2/6-311++G(2d, 2p) level [47], whereas in the present study H-bond distance and angle are 1.890 Å, 157.8° respectively. In other series such as **H-O-1**, **H-O-2**, **H-O-3a** and **H-O-4a** for the strongest and the weakest IE follows similar trend as observed in the case of **H-O-H** series. As size of alkyl group increases on H-bond donor, the strength of IE decreases, this can be observed by decreasing in O–H bond distances. In the case of **H-O-1**, **H-O-3a** and **H-O-4a** series have same distances for the strongest as well as for the weakest IE but their energies differ by $2.0\text{--}2.5 \text{ kJ mol}^{-1}$. When correlating the IE with H-bond length $\text{H}\cdots\text{O}$, the smallest distance of $\text{H}\cdots\text{O}$ not corresponds to the strongest IE but the longest distance of d ($\text{H}\cdots\text{O}$) corresponds to the weakest IE. The differences between the distances of strongest IE and smallest bond lengths are in the range $0.004\text{--}0.006 \text{ Å}$. Similar discrepancy can be observed by considering O–H \cdots O bond angle and are in the range of $3.73\text{--}4.87^\circ$ and their corresponding energies are in the range of $1.0\text{--}1.87 \text{ kJ mol}^{-1}$. The strength of IE can be compared with the elongation of C=O bond, longest distance of C=O bond (1.233 Å) corresponds to the strongest and shortest distance of C=O bond (1.225 Å) corresponds to weakest one for all H-bond donor series (**H-O-R**).

Topological parameters

In addition to the energetic and geometric analysis, we performed a topological study in order to correlate the strength of H-bond with increase the size of alkyl groups by using “atoms in molecules (AIM)” analysis. The AIM theory is first an extension of quantum mechanics to sub-domains properly defining an atom as an open system. It has also proven to be a useful and successful tool in the

interpretation of the charge density toward a wide variety of chemical concepts [44]. In **H-O-H** series, at O \cdots H bond bcp electron density is higher in **C-3**, **C-2** and lower in **N-4a** complexes whereas electron densities at O–H bond bcp are lower for **C-2**, **C-3** and higher for **N-4a**. As the size of alkyl group is increased on either “C” or “N” atom of amide, electron density is increased at O \cdots H bond bcp whereas it decreased at O–H bond bcp. The changes in electron densities are 0.001 a.u. at O \cdots H bond bcp and that of O–H bond bcp decreased to 0.002 a.u. In **H-O-1** series, at O \cdots H bond bcp, electron density is higher for **C-3** and lowers for **N-0** complexes and electron density decreases for **C-3**, and increased in **N-0** complexes at O–H bcp. Similar results are observed for remaining series. These results are in good agreement with strength of IE. Figure 3a–c shows the good correlation among the IE, H-bond distance and electron density at bcp; correlation values are in the range 0.73–0.84.

Harmonic vibrational frequencies

The harmonic vibrational frequencies and intensity of O–H \cdots O complexes were calculated at B3LYP/aug-cc-pVDZ level of theory. When the vibrational spectra of a free H–X group and those in X–H \cdots Y conventional H-bond are compared, it is generally observed that the H–X stretching vibration undergoes a substantial shift towards lower frequency and increase in intensity.

The O–H asymmetric stretching frequency for water is 3795 cm^{-1} and intensity is 4 km mol^{-1} . In **H-O-H** as H-bond donor series, the lowest O–H stretching frequency observed for **C-3** complex and the highest for **N-4a** complex. The frequencies are red shifted by formation of O–H \cdots O, frequency decreased to 3549, 3642 cm^{-1} and intensities increased to 600, 444 km mol^{-1} for **C-3** and **N-4a** complexes respectively. The red shift of O–H stretching frequency is consistent with the elongation of O–H bond. Similar results of O–H stretching frequency are also found in other complexes of this series, among these complexes the red shift of O–H stretching frequency is maximum in **C-3** complex (246 cm^{-1}), while it is minimum in **N-4a** complex (152 cm^{-1}). In **H-O-H** series, the red shift of the O–H stretching frequency follows similar order as we observed in strength of IE as well as O–H bond distances. While addition of methyl group to H-bond acceptor (**C-1** or **N-1** complexes), the strength of IE increases which can be observed by decrease in frequency to 3562, 3581 cm^{-1} from 3600 cm^{-1} (**N-0** complex) whereas intensities are increased from 479 km mol^{-1} (**N-0** complex) to 629, 610 km mol^{-1} for **C-1** and **N-1** complexes respectively. As the size of alkyl group increases on H-bond acceptor, frequency is decreased as compared to **N-0** complex but relative difference in frequency change is very low. Whereas **N-4a** complex have

higher frequency as compared to **N-0** complex (42 cm^{-1}). The alkyl groups attached to the “C” atom of amide has lower frequencies as compared to that of “N” atom of amide and these results are in good agreement with IE. Similar results are found in the **H-O-1**, **H-O-2** series except for **N-4a** complex. In **H-O-1** series, **C-3** has lower and **N-0** has higher frequencies, and frequency is red shifted by 257, 206 cm^{-1} respectively, and it is 256, 205 cm^{-1} for **H-O-2** series. The results in **H-O-3a**, **H-O-4a** series follows **H-O-1** series results except for **C-2** complex in **H-O-3a**. In all the complexes, maximum red shift of the O–H stretching frequency is found in **C-3**...**H-O-1** complex. These results are in good agreement with the strength and distances of H-bond.

Type-IIA complexes

Binding energies

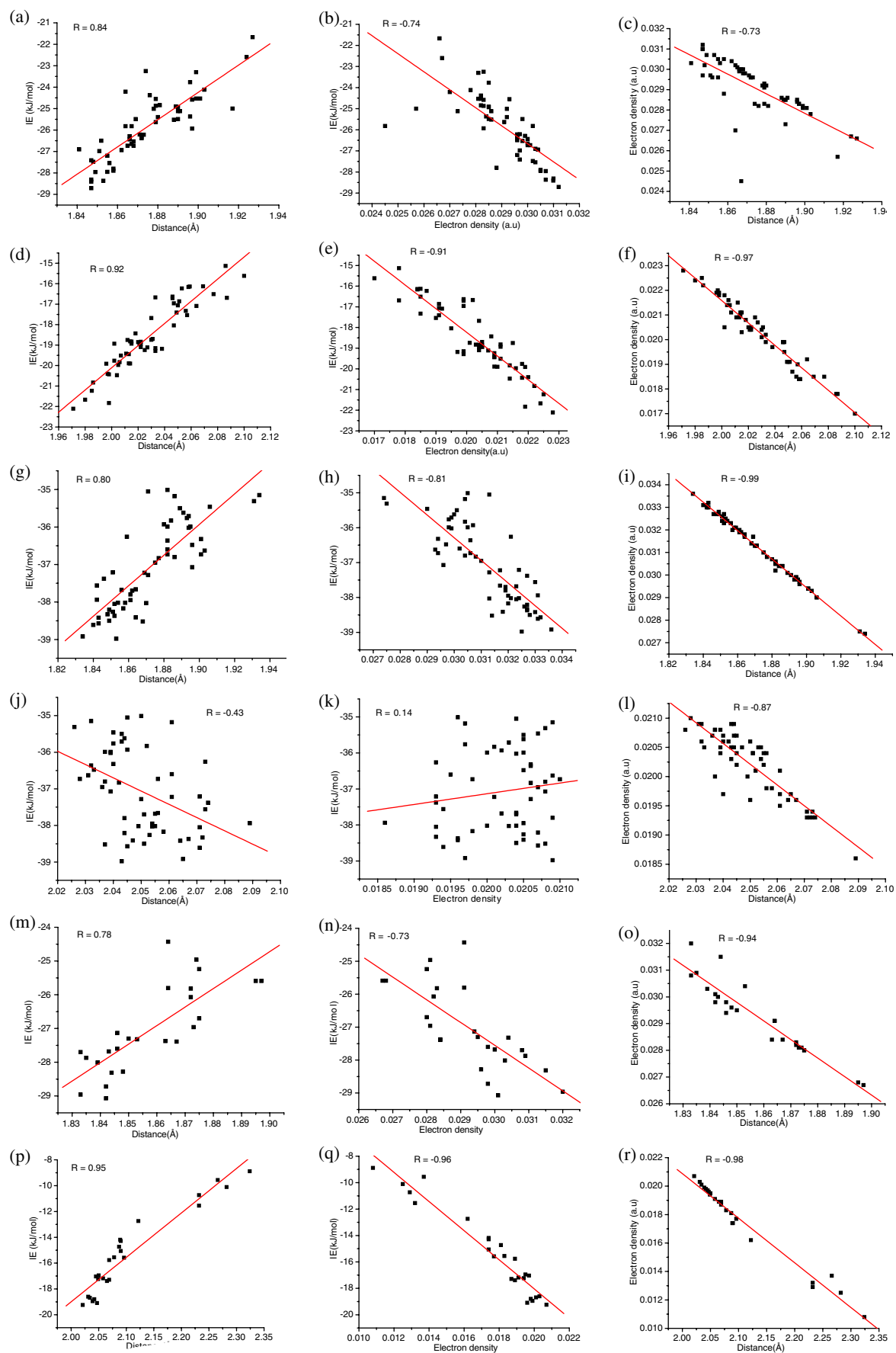
Figure 4a shows variation of IE as a function of increasing size of alkyl groups in Type-IIA complexes. The strongest H-bond is present in the **N-0**...**H-O-3a** complex ($-22.11\text{ kJ mol}^{-1}$) and the weakest in the **N-4a**...**H-O-H** ($-15.13\text{ kJ mol}^{-1}$). In **H-O-H** series, the strongest H-bond is observed for **N-0** and the weakest for **N-4a** complex while remaining complexes follows the order as **N-0**>**C-1**~**N-1**>**N-2**>**N-3**>**N-3a**~**C-2**~**C-3**~**C-3a**>**C-4a**>**N-4a**. Urban et al. [46] reported H-bond energy of formamide-water complex at MP2/6-311++G(2d, 2p) level as $-19.96\text{ kJ mol}^{-1}$ and in present study the IE is $-18.83\text{ kJ mol}^{-1}$. Complexes with methyl groups substituted at “C” atom ($-17.33\text{ kJ mol}^{-1}$) or “N” atom ($-17.41\text{ kJ mol}^{-1}$) of amide have low IE as compared to formamide-water complex ($-18.83\text{ kJ mol}^{-1}$). As the size of alkyl group increases from methyl to ethyl, a slight decrease in the IE ($0.3\text{--}1.5\text{ kJ mol}^{-1}$) is observed. The same trend is observed as size of alkyl group increases to n-propyl, i-propyl, t-butyl groups. In this series **N-4a** complex has the lowest IE ($3\text{--}4\text{ kJ mol}^{-1}$) when compared to formamide-water complex. As in **H-O-H** series, similar trend was observed for **H-O-1** and **H-O-2** series. Two exceptions from general trend are **N-3a** complex which has higher energy compared to **N-4a** and **C-4a** complex in **H-O-2** series, which is lower in energy compared to **N-4a** complex. In **H-O-1** and **H-O-2** series, the strongest IEs are observed for **N-0** complexes. The H-bond IE of formamide-methanol (**N-0**...**H-O-1**) reported by Fu et al. [35–38] at MP2/6-31 G(d,p) level is -24.2 kJ mol^{-1} . As the size of alkyl groups on H-bond donor is increased, the strength of H-bond decreases, which is observed in all H-bond donor series (Fig. 4a). Both **H-O-4a** and **H-O-2** series follow similar trend. Whereas in **H-O-3a** series, **N-3** has strong IE as compared to **N-1** and **N-2** complexes while **C-4a** has the lowest IE energy as compared to the

Fig. 3 (a), (d), (g), (j), (m), (p) show IE vs D; (b), (e), (h), (k), (n), (q) show IE vs ρ ; (c), (f), (i), (l), (o), (r) show ρ vs D. Here (a), (b), (c) for **IA**; (d), (e), (f) for **IIA**; (g), (h), (i) for **III** (O–H...O), (j), (k), (l) for **III** (N–H...O); (m), (n), (o) for **IB**; (p), (q), (r) for **IIB**. IE – interaction energy (kJ mol^{-1}), D – distance (Å), ρ – electron density at bcp (a.u)

remaining complexes of this series. An increase in the size of alkyl groups on H-bond acceptors also decreases the strength of H-bond and follows order **H-O-3a**>**H-O-4a**>**H-O-1**>**H-O-2**>**H-O-H**. In the case of H-bond acceptors, complexes with alkyl group substituted at “N” atom of amide have higher IE than that of the “C” atom of amide except in **H-O-3a** and **H-O-4a** series of complexes (Fig. 4a). The bond strengths of the non-bonded interactions are greatly influenced by the size and the neighboring non-bonded interactions [48–50]

Geometrical parameters

Figure 4b and c reflects the variation of various principal geometrical parameters of the complexes as function of the size of alkyl groups. In **H-O-H** series, the smallest $d(\text{N–H}\cdots\text{O})$ (2.015 Å) corresponds to the strongest IE ($-22.11\text{ kJ mol}^{-1}$) and the longest $d(\text{N–H}\cdots\text{O})$ (2.086 Å) corresponds to the weakest one ($-15.13\text{ kJ mol}^{-1}$). Substitution of methyl group at “C” or “N” atom of amide decreases IE, this correlating with increasing N–H...O bond distance. The relative distances of **C-1** and **N-1** complexes with **N-0** complexes are 0.041 and 0.034 Å respectively. The decrease in strength of remaining complexes of this series can be attributed by increasing N–H...O bond distance as compared to the **N-0** complex. Allinger et al. reported H-bond distance and angles of **N-0-H-O-H** complex is 2.006 Å and 178.0° respectively at MP2/6-311++G(2d, 2p) level [46] whereas in the present study H-bond distance and angle are 2.015 Å , 179.8° respectively. In other series such as **H-O-1**, **H-O-2**, **H-O-3a** and **H-O-4a** strong and weak IE follows similar trend as observed in **H-O-H** series. As size of alkyl group increases on H-bond acceptor, the observed strength of IE is consistent with N–H...O bond distances. When we correlate the IEs with N–H distance, the smallest distance of $d(\text{N–H})$ corresponds to the weakest IE and the longest distance of N–H corresponds to the strongest IE except for **N-3a** complexes. In all series of complexes, the weakest H-bond complexes (**N-4a**, **C-4a** complexes) have large deviation in O–H...O bond angle to linearity (180°) and for remaining complexes O–H...O angles are close to linearity however it is not correlated with strength of IE. The strength of IE can be compared with the elongation of C=O bond, longest distance of C=O bond corresponds to the weakest and shortest distance of C=O bond corresponds to the strongest one. Alkyl groups substituted at



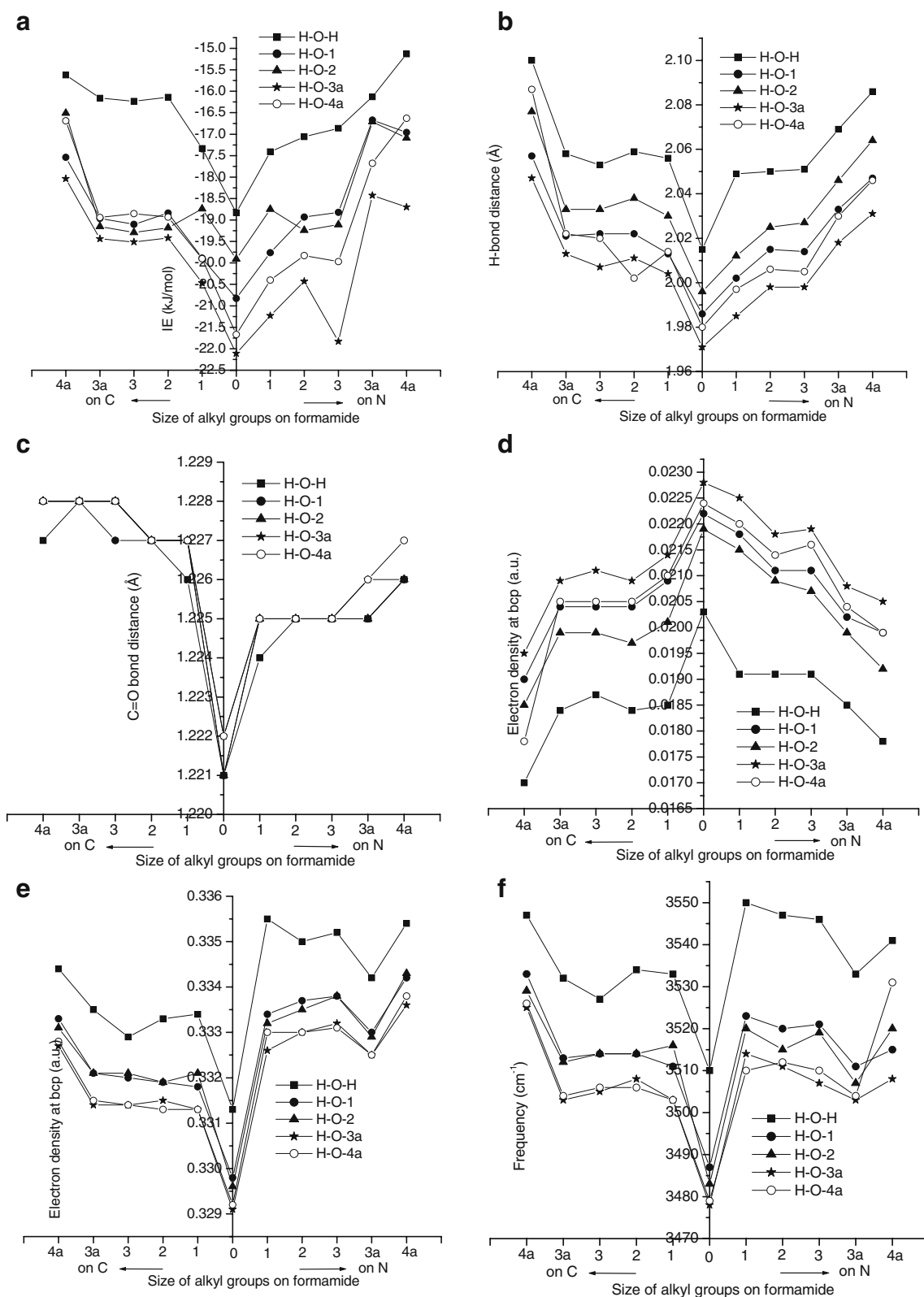


Fig. 4 Variation of (a) IEs (b) H-bond distance (c) C=O bond distance (d) ρ at O \cdots H bond bcp (e) ρ at N–H bcp (f) N–H stretching frequency with size of alkyl groups in Type-IIA complexes

“N” atom of amide forms strong H-bond complex as compared to “C” atom of amide. This can be notified by shortening of C=O bond lengths in alkyl groups substituted at “N” atom of amide as compared to “C” atom of amide (Fig. 4b and c). For the strongest IE, C=O distance is 1.221 Å in **H-O-H**, **H-O-1**, and **H-O-2** series of complexes while it is 1.222 Å in **H-O-3a** and **H-O-4a** series of complexes. In the case of the weakest H-bond complexes, C=O bond length is 1.228 Å for all H-bond acceptor series (**H-O-R**) except for **H-O-H**, and it is decreased to 1.227 Å.

Topological parameters

Electron density at N–H and O⋯H bcp are given in Fig. 4d and e. In **H-O-H** series of complexes, at O⋯H bond bcp, electron density is higher in **N-0** and lower in **C-4a** complexes while the electron densities at N–H bond bcp are lower for **N-0** and higher for **N-4a** instead of **C-4a**, differ by 0.0014 a.u. As the size of alkyl group is increasing on either “C” or “N” atom of amide, electron density is decreased at O⋯H bond bcp while it increased at N–H bond bcp. The electron density at O⋯H and N–H bond bcp is more for alkyl groups substituted “N” atom of amide as compared to that of “C” atom of amide. Similar results are observed for remaining series (**H-O-1**, **H-O-2**, **H-O-3a**, and **H-O-4a**), at O⋯H bond bcp electron density is higher for **N-0** and lower for **C-4a** complexes while electron density decreases for **N-0**, and increases in **N-4a** complexes at O–H bcp. These results are in good agreement with strength of IEs. Figure 3d–f shows the correlation among the IE, H-bond distance and electron density at bcp, their correlation values are in the range 0.91–0.97.

Harmonic vibrational frequencies

The N–H symmetric frequency of formamide is 3569 cm^{−1} and intensity is 32 km mol^{−1}. For **H-O-H** series, the lowest N–H symmetric stretching frequency is observed for **N-0** complex and the highest for **C-4a** complex (Fig. 4f). The frequencies are red shifted by formation of N–H⋯O hydrogen bond, frequency decreased to 3510, 3547 cm^{−1} and intensities increased to 264, 154 km mol^{−1} for **N-0** and **C-4a** complexes respectively. The red shift of N–H stretching frequency is consistent with the elongation of N–H bond. Similar results of N–H stretching frequency are also found in other complexes of this series. In **H-O-H** series, the red shift of N–H stretching frequency follows similar order as we observed in strength of IE as well as N–H bond distances. In all the complexes, maximum red shift of the N–H stretching frequency is found in **N-1**⋯**H-O-4a** complex. Addition of methyl group to H-bond acceptor (**C-1** or **N-1** complexes), the strength of H-bond decreases

which can be observed by increase in frequency to 3533, 3550 cm^{−1} from 3510 cm^{−1} (**N-0** complex) whereas intensities are changed to 203, 293 km mol^{−1} from 264 km mol^{−1} (**N-0** complex) for **C-1** and **N-1** complexes respectively. In all series of complexes as the size of alkyl group increases on H-bond donor, frequency is increased as compared to **N-0** complex. As the size of alkyl group increases on H-bond acceptors, N–H stretching frequencies decreased as compared to formamide-water complex. In **H-O-1** series, **N-0** has lower and **C-4a** has higher frequencies, and frequency is red shifted by 82, 55 cm^{−1} respectively. Similar results are found in remaining series such as **H-O-2**, **H-O-3a** and **H-O-4a** series (Fig. 4f).

Type-III complexes

Binding energies

Complexes of Type-III are characterized by two H-bonds with both C=O and N–H groups of formamide participating simultaneously in H-bond. In the **H-O-R** series, an increase in the size of the alkyl substituent decreases the strength of the H-bond, a trend similar to one observed in Type-IA complexes. In **H-O-H** series of complexes, the strongest H-bond formed by **C-4a** (−38.92 kJ mol^{−1}) complex whereas the weakest by **N-0** (−36.60 kJ mol^{−1}) complex. In **H-O-H** series, as the size of alkyl groups increases the strength of IE increases as compared to formamide-water complex and follows the order as **C-4a** > **C-3a** > **C-1** ~ **N-3a** > **N-1** ~ **N-2** > **N-4a** > **C-3** > **C-2** > **N-3** > **N-0** (Fig. 5a). In **H-O-1** series of complexes, the strongest IE is observed in **C-1** complex (−38.98 kJ mol^{−1}) and the weakest in **N-0** complex (−37.07 kJ mol^{−1}). In this series, alkyl groups substituted at “C” atom of amide forms more stable complex when compared to the “N” atom of amide, except for **N-2** complex. Similar results are obtained in **H-O-2** series, wherein **C-4a** forms more stable complex. In **H-O-3a** series of complexes, alkyl groups substituted at “N” atom of amide forms more stable complex compared to “C” atom substituted complexes except for **C-4a** complex, which is more stable in this series. In **H-O-4a** series, as the size of alkyl groups increase the strength of IE decreases, the strongest IE is observed for **C-1** complex whereas the weakest for **C-4a** complex.

Geometrical parameters

Figure 5b–5d reflects the variation of various principal geometrical parameters of the complexes as function of the size of alkyl group. The strength of IE can be correlated with O–H⋯O and N–H⋯O distances. In **H-O-H** series, the smallest *d*(O–H⋯O) (1.834 Å) corresponds to the strongest IE and the longest *d*(O–H⋯O) (1.882 Å) corre-

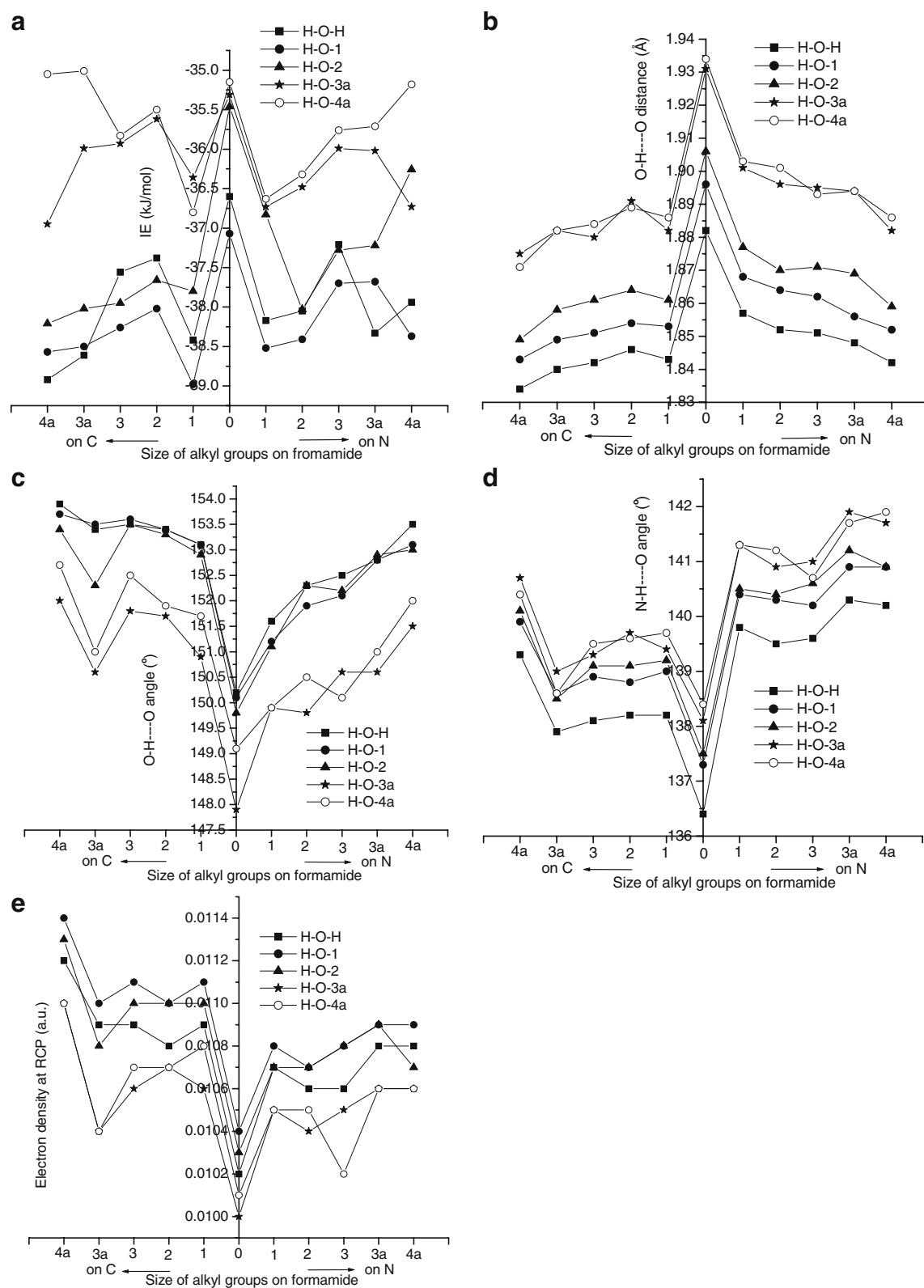


Fig. 5 Variation (a) IEs (b) O-H...O bond distance (c) O-H...O bond angle (d) N-H...O bond angle (e) ρ at RCP with size of alkyl groups in Type-III complexes

sponds to the weakest one. As the size of alkyl group increases on $R\text{-CONH-R}^1$, distance of $\text{O}\cdots\text{H}\cdots\text{O}$ bond decreases whereas $\text{N-H}\cdots\text{O}$ bond length increases (except for **N-1**). The strength of IE increases when methyl group is substituted at “C” or “N” atom of amide, which can be correlated with decrease in $\text{O-H}\cdots\text{O}$ bond distance. The $\text{O-H}\cdots\text{O}$ bond distances are smaller in **H-O-H** series as compared to remaining series of complexes whereas $\text{N-H}\cdots\text{O}$ bond lengths are larger than remaining series of complexes. These results are in good agreement with strength of IE when compared to the remaining series of complexes, except **H-O-1** series, which forms the strongest H-bonds. In other series such as **H-O-1**, **H-O-2**, **H-O-3a** and **H-O-4a** for the strongest and the weakest IE follows similar trend as observed in **H-O-H** series. As size of alkyl group increases on **H-O-R**, the observed strength of IE is consistent with $\text{O-H}\cdots\text{O}$ bond distances. In all series of complexes, the weakest H-bond complexes (**N-0** complex) have large deviation in $\text{O-H}\cdots\text{O}$, $\text{N-H}\cdots\text{O}$ bond angles to linearity (180°) and for remaining complexes these angles are close to linearity however $\text{N-H}\cdots\text{O}$ is not correlated with strength of IE. As the size of alkyl groups increases on **H-O-R**, order of IE of complexes is governed by C=O group as compared to N-H group.

Topological parameters

Electron densities at ring critical point (ρRCP) are shown in Fig. 5e for the bonds involved in H-bond formation ($\text{O}\cdots\text{H-O}$ and $\text{O}\cdots\text{H-N}$ bonds). It is well-known that the electron density at $\text{Y}\cdots\text{H}$ (Y is the accepting center within the $\text{Y}\cdots\text{H-X}$ bridge) correlates with H-bond energy; thus the stronger the H-bond, the greater the $\rho_{\text{Y}\cdots\text{H}}$ value [53–55]. Such a relationship is mainly fulfilled for homogeneous samples [56]. All the results presented here indicate that $\text{O}\cdots\text{H-O}$ bonds are stronger than $\text{O}\cdots\text{H-N}$ bonds. It was shown that for intermolecular H-bonds, greater ρRCP values are observed for stronger H-bonds [57]. For such

systems RCP are associated with the ring created due to intermolecular H-bond formation. In the present study, RCP is created by two intermolecular H-bonds ($\text{O}\cdots\text{H-O}$ and $\text{O}\cdots\text{H-N}$ bonds) formed by C=O and N-H groups. For all series of complexes the strength of IE is well correlated with ρRCP . Similar correlation is found while considering electron density at $\text{O}\cdots\text{H}$ bcp of $\text{O}\cdots\text{H-O}$ bond. In **H-O-H** series of complexes, **C-4a** has high electron density whereas **N-0** has low electron density at ρRCP . Electron density of alkyl groups substituted at “C” atom of amide is more than that of “N” atom substituted alkyl groups. Similar results are observed for remaining series of complexes and in good agreement with strength of IE. A close look at Type – III complexes reveal that correlations among the IE, H-bond distance and electron density at bcp are better for $\text{O}\cdots\text{H-O}$ bond than that of $\text{O}\cdots\text{H-N}$ bond (Fig. 3g-l). The IE is contributed by both H-bonds, when considering average distance and sum of electron density of $\text{O}\cdots\text{H-O}$ and $\text{O}\cdots\text{H-N}$ bonds an increasing of correlation coefficient (0.78–0.85) is observed (Fig. 6). These values are much closer to $\text{O}\cdots\text{H-O}$ bond correlation values, indicating the order of IE of complexes is governed by C=O group as compared to N-H group. Correlation of IE with electron density at RCP has less compared to the sum of electron densities.

Harmonic vibrational frequencies

The N-H symmetric stretching frequency of formamide is 3569 cm^{-1} and intensity is 32 km mol^{-1} . In **H-O-H** series, lowest N-H and O-H frequencies correspond to stronger H-bond complex (**C-4a**) while high frequencies correspond to weaker H-bond complexes (**N-0**). The frequencies are red shifted by formation of two intermolecular ($\text{O-H}\cdots\text{O}$ and $\text{N-H}\cdots\text{O}$) H-bonds, frequencies decreased to 3501 , 3459 cm^{-1} and intensities increased to 696 , 127 km mol^{-1} for **C-4a**. For **N-0** complex these values are 3540 , 3475 cm^{-1} and 510 , 44 km mol^{-1} respectively. The red shift of N-H and

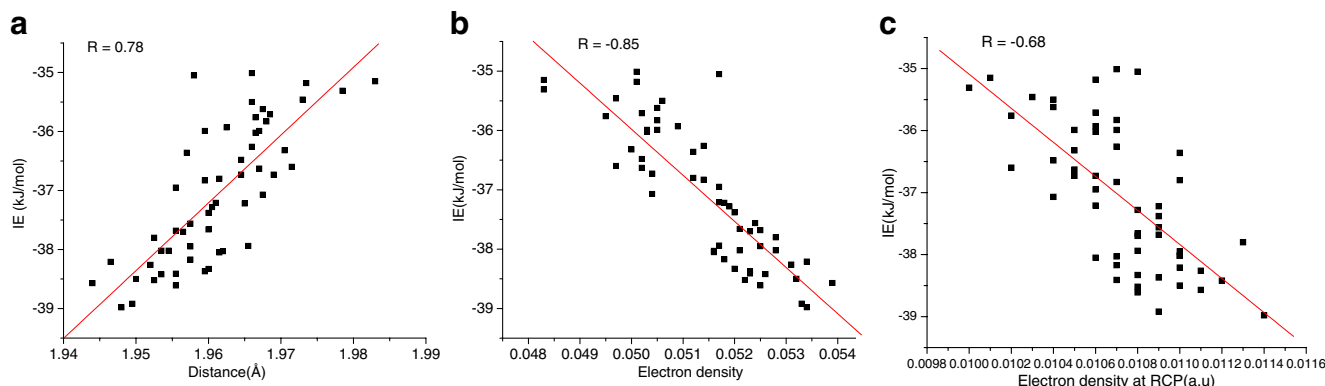


Fig. 6 (a) IE vs average distance (b) IE vs sum of electron density (c) IE vs electron density at RCP of complexes Type-III wherein $\text{O-H}\cdots\text{O}$ and $\text{N-H}\cdots\text{O}$ bonds average distance and summation of electron density were considered

O–H stretching frequency is consistent with the elongation of N–H and O–H bonds. Similar results of the N–H and O–H stretching frequency are also found in other complexes of this series. In **H–O–H** series, the red shift of O–H (N–H) stretching frequency follows similar order as observed in strength of IE as well as O–H (N–H) bond distances. As the size of alkyl group increases on R-CONH-R¹, frequency is decreased as compared to **N–0** complex but relative difference in frequency change is very low. As the size of alkyl groups increases on **H–O–R**, the stretching frequencies of O–H and N–H bonds increased as compared to formamide-water complex. In all series of complexes, O–H stretching frequencies follows similar results as found in **H–O–H** series of complexes while it is not established in N–H frequencies. However N–H frequencies are decreased and

intensities increased in the complex form as compared to that of monomers. The strength of H-bonds are much closer to ordering of O–H bond frequencies (intensities) as compared to that of N–H bond. This shows that O–H forms strong H-bond as compared to N–H bond.

Type-IB complexes

Binding energies

Figure 7a shows the variation of IEs with increasing size of alkyl groups on formamide. The strongest IE ($-29.07 \text{ kJ mol}^{-1}$) is present in the **N-3-C-3...H-O-1** complex and the weakest ($-24.43 \text{ kJ mol}^{-1}$) in the **N-4a-C-4a...H-O-4a**. In **H–O–H** series, the strongest energy complex is observed

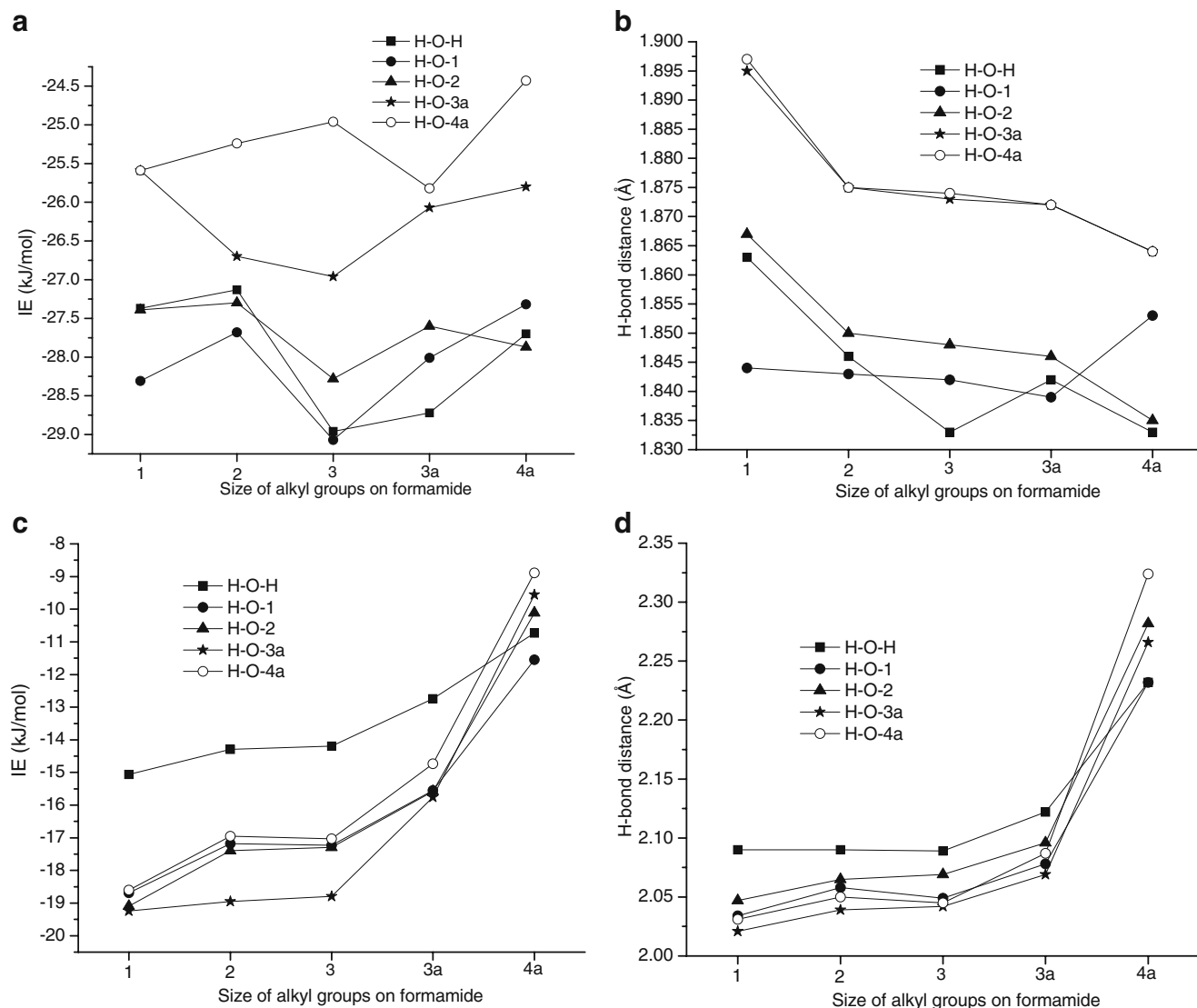


Fig. 7 Variation of IEs, X–H...Y bond distance with increasing the size of alkyl groups on formamide: (a), (b) in Type-IB complexes and (c), (d) in Type-IIB complexes respectively

for **N-3-C-3** and the weakest for **N-2-C-2**. Dannenberg et al. [32] reported H-bond energy of **N-1-C-1**⋯**water** complex at B3LYP/D95++G(d, p) level as $-22.47 \text{ kJ mol}^{-1}$ and in present study the IE is $-27.37 \text{ kJ mol}^{-1}$. **N-1-C-1** complex has less IE than **C-1** and more than **N-1** complexes formed by Type-IA complexes. It is observed that in all the series show an increase in the IE when the size of alkyl substituent increases from methyl to ethyl to n-propyl. The n-propyl substituent complexes (**N-3-C-3**) in most of the series show the highest IE. Further increase in the size of alkyl substituent (i-propyl, t-butyl) leads to decrease in the IE. In **H-O-4a** series, **N-3a-C-3a** has more IE than **N-3-C-3** complex. As the size of alkyl groups increases on H-bond donor, the strength of H-bond decreases except for **H-O-1** wherein H-bond strength increases.

Geometrical parameters

Figure 7b shows the variation of O–H⋯O bond distance with increasing size of alkyl groups on formamide. The strength of IE is correlated with O–H distance. In **H-O-H** series, the largest $d(\text{O–H})$ corresponds to the strongest IE and the smallest $d(\text{O–H})$ corresponds to the weakest one and their corresponding distances are 0.980, 0.977 Å respectively. In other series such as **H-O-1**, **H-O-2**, **H-O-3a** and **H-O-4a** for strong and weak IEs follows similar order as observed in the case of **H-O-H** series. It is observed that IEs are correlating with H-bond H⋯O distance; the smallest distance of H⋯O not corresponds to the strongest H-bond and vice versa. Similar discrepancy is observed by considering O–H⋯O bond angle and C=O distances.

Topological parameters

The electron densities at bcp of O–H bond are well correlated with strength of IE, low electron density corresponds to the strongest IE and high electron density corresponds to the weakest one except for **H-O-1** series of complexes wherein **N-1-C-1** has low electron density at O–H bcp. In **H-O-1** series, the electron density difference between **N-1-C-1** and the strongest complex is 0.0011 a.u. Similar results are observed in other series of complexes.

Harmonic vibrational frequencies

In **H-O-H** series, the lowest O–H asymmetric stretching frequency is observed for **N-3-C-3** complex and highest for **N-1-C-1** complex. The frequencies are red shifted by formation of O–H⋯O, frequency decreased to 3530, 3591 cm^{-1} and intensities increase to 709, 598 km mol^{-1} for **N-3-C-3** and **N-1-C-1** complexes respectively. The red shift of O–H stretching frequency is consistent with the

elongation of O–H bond. Similar results of O–H stretching frequency are also found in other complexes of this series, among these complexes the red shift of O–H stretching frequency is maximum in **N-3-C-3** complex (265 cm^{-1}), while it is minimum in **N-1-C-1** complex (204 cm^{-1}). In **H-O-H** series, the red shift of O–H stretching frequency follows similar order as we observed in the case of IE as well as O–H bond distances. Similar results are found in other series of complexes except for **N-1-C-1**⋯**H-O-1** complex wherein O–H stretching frequency is low as compared to that of **N-3-C-3**⋯**H-O-1** complex.

Type-IIB complexes

Binding energies

The strongest IE ($-15.06 \text{ kJ mol}^{-1}$) is present in **N-1-C-1**⋯**H-O-3a** complex and the weakest ($-10.06 \text{ kJ mol}^{-1}$) in **N-4a-C-4a**⋯**H-O-4a** (Fig. 7c). Dannenberg et al. [32] reported H-bond energy of **N-1-C-1**⋯**H-O-H** complex at B3LYP/D95++G(d, p) level as $-12.09 \text{ kJ mol}^{-1}$ and in present study the IE is $-15.06 \text{ kJ mol}^{-1}$. In **H-O-H** series of complexes **N-1-C-1** has strong IE whereas **N-4a-C-4a** has weak IE. As the size of alkyl group increases on H-bond donor, strength of IE decreases as compared to **N-1-C-1** complex. Similar results are found in other series of complexes. As the size of alkyl group is increased on **H-O-R**, the strength of H-bond increases as compared to water as H-bond acceptor, lowest complex formed with **H-O-3a**. In **H-O-4a** series the H-bond strength decreases as compared to that of **H-O-3a**, but form stronger H-bond complexes as compared to that of water system. As the size of alkyl groups

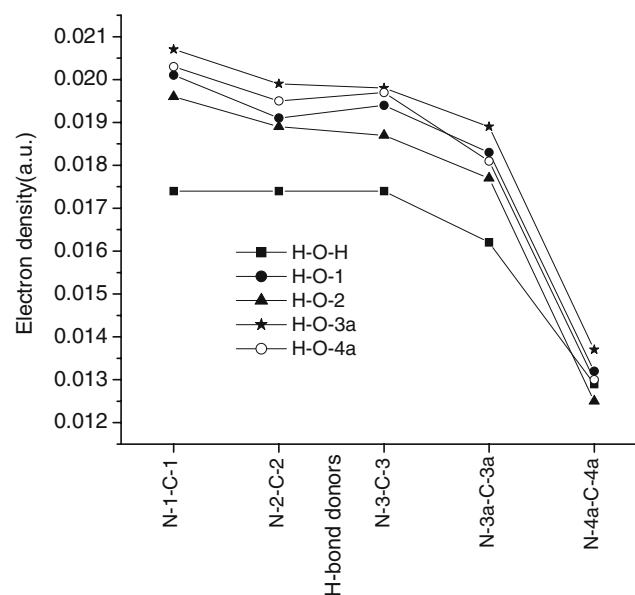


Fig. 8 Electron density of Type-IIB complexes calculated at O⋯H bond bcp using AIM program

increases on H-bond acceptor, H-bond strength follows order **H-O-3a**>**H-O-2**~**H-O-1**>**H-O-4a**>**H-O-H**.

Geometrical parameters

In **H-O-H** series, the shortest $d(\text{H}\cdots\text{O})$ (2.090 Å) corresponds to the strongest H-bond and the longest $d(\text{H}\cdots\text{O})$ (2.232 Å) corresponds to the weakest one (Fig. 7d). As the size of alkyl groups increasing on H-bond donors, the strength of IE decreases, it is correlating with increasing in $\text{H}\cdots\text{O}$ bond distance. In other series such as **H-O-1**, **H-O-2**, **H-O-3a** and **H-O-4a** for strong and weak IE follows similar trend as observed in **H-O-H** series. Increase of H-bond strength with size of alkyl groups on H-bond acceptor correlating with decrease in $\text{H}\cdots\text{O}$ bond length. When correlating IE with H-bond angle $\alpha(\text{N-H}\cdots\text{O})$, closer to linear angle (180°) corresponds to stronger H-bond and large deviation from linearity corresponds to weaker H-bond.

Topological parameters

The electron densities at $\text{O}\cdots\text{H}$ bond bcp are well correlated with the strength of IE, high electron density corresponds to the strongest IE and low electron density corresponds to the weakest one. In **H-O-H** series of complexes, **N-1-C-1** has high electron density at $\text{O}\cdots\text{H}$ bcp (0.0174 a. u.) and **N-4a-C-4a** complex has low electron density (0.0129 a. u.). In all series of complexes **N-3a-C-3a** has high electron density at $\text{O}\cdots\text{H}$ bcp (0.0207 a.u.). The ordering of electron density at $\text{O}\cdots\text{H}$ bcp is consistent with ordering of H-bond acceptors strength (Fig. 8). The decrease in electron density at N–H bcp is correlated with strength of H-bond except for **N-3a-C-3a** complex. Type-IB, IIB complexes have good correlation among the IE, electron density and H-bond distance (Fig. 3m-r).

Harmonic vibrational frequencies

In **H-O-H** as H-bond donor series, lowest N–H stretching frequency do not correspond to stronger IE but high frequency corresponds to weaker one. However N–H frequencies are red shifted by formation of $\text{N-H}\cdots\text{O}$ bond. A decrease in frequency and an increase in the intensities are observed as compared to N–H frequencies of uncomplexed form. Similar results are found in other series of complexes. As the size of alkyl group is increased on H-bond acceptor, the strength of H-bond is correlated well with decrease in N–H stretching frequency. Among all series of complexes **H-O-3a** series has lower frequency then followed by **H-O-4a** and least for **H-O-H** series of complexes. These results are in good agreement with IE of H-bond acceptors order, **H-O-3a**>**H-O-4a**>**H-O-1**~**H-O-2**>**H-O-H**.

Conclusions

This paper provides the effect of alkyl substitution (CH_3 , C_2H_5 , $n\text{-C}_3\text{H}_7$, $i\text{-C}_3\text{H}_7$, and $t\text{-C}_4\text{H}_9$) on H-bond strength of substituted amide-alcohol complexes by using quantum mechanical methods. The following conclusions were drawn from the current study,

1. In Type-IA complexes C=O group of **C-3** form more stable complex with **H-O-1** whereas in Type-IIA complexes, **N-0** form strong H-bonds with **H-O-3a**. However Type-III systems form more stable complexes as compared to other types of complexes.
2. When C=O group is participating in H-bond, the strength of H-bond decreases with increasing size of alcohols except for **H-O-1** (Type-IA, Type-III and Type-IB complexes). But it increases with increasing size of alkyl groups on amide and decreases with bulky groups.
3. In the case of N–H group as H-bond donor, the strength of H-bond increases with increasing size of alcohols (Type-IIA and Type-IIB complexes) whereas decreases with increasing size of alkyl groups on H-bond donors.
4. Type-IA, IIA complexes exhibit good correlations among IE, H-bond distance and electron density at bcp, corresponding values are in the range 0.74–0.84 and 0.91–0.97 respectively.
5. In Type-III complexes correlations among the IE, H-bond distance, and electron density at bcp are better for $\text{O}\cdots\text{H-O}$ bond than that of $\text{O}\cdots\text{H-N}$ bond. While considering average distance and sum of electron density of $\text{O}\cdots\text{H-O}$ and $\text{O}\cdots\text{H-N}$ bonds an increasing of correlation coefficient (0.78–0.85) is observed. These values are much closer to $\text{O}\cdots\text{H-O}$ bond correlation values, indicating the order of IE of complexes is governed by C=O group as compared to N–H group.
6. In Type-III complexes, correlation of IE with electron density at RCP is less compared to sum of electron densities.
7. Good correlation is observed among the IE, electron density and H-bond distance for Type-IB, IIB complexes in the range 0.73–0.94 and 0.95–0.98 respectively.
8. Because the amide linkage is an important building block in drugs like paracetamol, phenegan, carbacephem, penicillin etc. One can tune the interaction between drugs and receptor by substituting alkyl groups on drug molecules according to the availability of hydrophobic space in the receptor. In this way, the results presented in this paper will be usefull in drug optimization process.

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