The proton affinities of a sequence of β-substituted acrylamide in the ground state: A DFT based computational approach

Biswarup Mandal[1], **Umasankar Senapati**[2], **Bhudeb Ranjan De**[1]✉

[1]Department of Chemistry and Chemical Technology, Vidyasagar University, Midnapore, W.B., India, Pin – 721102, *E-mail*: biswarupmandal75@gmail.com

[2]Department of Chemistry, Belda College, Belda, Paschim Medinipur, Pin- 721424, W.B., India, *E-mail*: Senapatiumasankar@gmail.com

✉**Corresponding author:**
Prof. Bhudeb Ranjan De,
E-mail: biswarupmandal75@gmail.com

Article History
Received: 16 June 2020
Accepted: 29 July 2020
Published: August 2020

Citation
Biswarup Mandal, Umasankar Senapati, Bhudeb Ranjan De. The proton affinities of a sequence of β-substituted acrylamide in the ground state: A DFT based computational approach. *Drug Discovery*, 2020, 14(34), 238-245

 I ISSN 2278–540X; EISSN 2278–5396

General Note
Article is recommended to print as color version in recycled paper. *Save Trees, Save Climate*.

ABSTRACT

A detailed study of the proton affinities of a series of β-substituted acrylamides and their O-protonated counterparts has been performed by B3LYP (DFT) method using 6-311G (d,p) basis sets with complete geometry optimization both before and after protonation. The gas phase O-protonation is observed to be exothermic and the local stereochemical disposition of the proton is found to be almost the same in each case. The presence of β-substituent is seen to cause very little change of the proton affinities, relative to the unsubstituted acrylamides. Computed proton affinities are sought to be correlated with a number of computed system parameters such as the Mulliken net charge on the carbonyl oxygen of the unprotonated bases, Mulliken net charge on the carbonyl oxygen and Mulliken net charge on the proton of the protonated bases. The overall basicity is explained by the distant atom contribution in addition to the contribution from the carbonyl group. The electron-releasing substituents are seen to increase the computed proton affinities (PAs) while the electron-withdrawing groups have an opposite effect as expected.

Keywords: B3LYP DFT; GAUSSIAN; Acrylamides; Charge distribution; Gas phase

1. INTRODUCTION

The acid base interactions are of great importance in chemistry. These quantitative studies in the gas phase methods (Bhome et al., 1973; Beauchamp et al., 1974; Yamadagni et al., 1973; Bhome et al., 1974; Solomon et al., 1974; Long et al., 1974; Brauman et al., 1970; Wieting et al., 1974; Staley et al., 1975) have the advantage of determining the intrinsic ground state acid base properties in the absence of complicating effects of solvation. For molecules containing carbonyl chromophores, protonation and hydrogen bonding are very much important. Recently the basicities of a series of substituted crotonaldehyde and acetophenone in their ground states have been theoretically calculated (Pandit et al., 2006; Senapati et al., 2008). The systems were aliphatic and aromatic conjugated carbonyl systems. In an effort to understand the nature and origin of variation in the relative magnitude of the proton affinities to be expected in a series of aliphatic carbonyls, namely, acryl amides, producing neurotoxicity in exposed humans and laboratory animals, we have calculated the gas phase ground state proton affinities of a number of β-substituted acrylamides by B3LYP(DFT) method using 6-311G(d,p) basis sets (Frisch et al., 2004; Lee et al., 1988; Becke et al., 1993). We have analysed the computed proton affinity values (PAs) to understand whether the pre-protonation charge distribution local to the chromophore or post-protonation relaxation of charge density or both are important in shaping the overall basicity of the acrylamides. We have also looked into the possible origin of the small shift in the proton affinities as one goes from the unsubstituted to the β-substituted acrylamides. In a particular state the possibility of correlating the proton affinity with the global hardness of the molecules is also explored. We have also calculated an important parameter softness to account for the stability of a molecule and the direction of acid-base reactions.

2. COMPUTATIONAL DETAILS

Calculations were performed using Gaussian 03W software and B3LYP (DFT) method with 6-311G (d,p) basis sets. In all calculations complete geometry optimizations has been carried out on the molecules both before and after protonation.

3. RESULT AND DISCUSSION

The molecules studied theoretically are β-substituted acrylamides and its protonated species. The molecules studied are listed in table 1 along with their respective abbreviated names and computed total energies and proton affinities in DFT method using 6-311G (d,p) basis set. Table 2 reports the computed Mulliken net charge on the carbonyl oxygen atoms at the equilibrium ground state of the unprotonated free base molecules as well as the computed Mulliken net charge carried out by proton and the Mulliken net charge on the carbonyl oxygen at the equilibrium ground state of the protonated bases. Atomic charge is not an observable quantum mechanical property. All methods for computing the atomic charges are necessarily arbitrary. Electron density among the atoms in a molecular system is being partitioned. Mulliken population analysis computes charges by dividing orbital overlap equally between the two atoms involved. Therefore the values are non-unique. Still, it is widely used. From table 1 it is seen that the proton affinities (PAs) of all the β-substituted acrylamides are in the range -0.2664 to -0.3654 hartree. Proton affinities (PAs) of all the β-substituted acrylamides indicate that the gas phase O-protonation is exothermic in each case. The electron-releasing substituents are seen to increase the computed PAs while electron-withdrawing groups have an opposite effect as expected. Table 1 reveals that proton affinity is highest for βAACR, X = -NH_2. From table 4 it is clear that lower softness value of βAACR, X = -NH_2 and highest softness value of βNACR, X = -NO_2 indicates βAACR is a hard base and favours protonation (since H^+ is a hard acid). This is one of the reasons of highest PA of βAACR. A perusal of table 2 reveals that the computed net charge on the proton is small in each case and is in the range 0.2864 to 0.3651 showing that a rather large migration of electron density to the added proton has taken place. The proton adds to the base, giving polar covalent sigma bond with a very extensive charge transfer. The base molecule carries the rest of the positive charge. The large degree of charge transfer results from the fact that H^+ is a bare nucleus, with a very low energy unfilled 1S orbital. That these migrations is not local and originates from all over the molecule is clearly reflected in the computed net charges on the carbonyl oxygen atom of the protonated bases as shown in table 2. The oxygen atom still carries a net negative charge, albeit depleted, relative to the unprotonated base. It is also seen that the charge density of O-atom before protonation is higher when X is an electron-releasing group. This favours protonation. The reverse is the case with electron-attracting group. This may be one of the reasons for the slight increase and decrease of PA values relative to unsubstituted acrylamides. It can therefore, be anticipated that the proton affinities of these carbonyl bases cannot be modelled or described by local properties of the carbonyl moiety only. It must be shaped strongly by distant atom contribution in addition to the contribution from the carbonyl group.

The local characteristics at or around the carbonyl moiety cannot model the substituent effects. This is again revealed from the data reported in table 3 where some of the selected computed geometrical parameters around the carbonyl group are listed. The O–H^+ bond length has a variation in the range 0.9669 to 1.4448 Å for all the protonated bases. The C–O–H^+ bond angle is virtually within 102.8165 – 116.1180° in all the cases. Similarly, the torsion angle τ (C–C–O–H^+) shows only a small variation in all the cases. The C–O length of all

the protonated bases increase except for βMyACR where it is same after protonation. The carbonyl ring near invariant stereochemistry around the protonation site of each base tends to suggest that the entire contribution from substituent effects to PA cannot be modelled properly unless contribution from far away centers are taken into account. It also points to the fact that "local" effects of the group must be very nearly identical in each case.

As the local parameter we have chosen the computed net charge density on the carbonyl oxygen atom of the unprotonated bases (q_{O^-}) and the net charge density on the proton (q_{H^+}) of the fully relaxed BH^+. It is seen that the plot of the computed gas phase proton affinities (PAs) against the computed net charge density on the carbonyl oxygen atom of the unprotonated bases (q_{O^-}) (figure 1) is not linear. It is also seen that the plot of the computed gas phase proton affinities (PAs) versus q_{H^+} of the fully relaxed BH^+ (figure 2) is not linear. We have also searched for the possibility of existence of correlation with a single global parameter of the entire molecule. As the global parameter we have chosen the hardness, $\eta = (I - A)/2 = (\varepsilon_{LUMO} \sim \varepsilon_{HOMO})/2$ listed in tables 4. It is seen that no perfect correlation between the hardness and proton affinity in the series could be made. This is further revealed from figure 3 where the gas phase proton affinity versus computed hardness is plotted which shows no linearity. Thus all these reveal marginal linearity of the computed PA's with respect to local and global parameters. This indicates that both pre- and post-protonation correlations with local charge densities in the immediate neighbourhood of the protonation site are weak.

Table 1

Computed total energy (hartree) of free base (B) and O- protonated base (BH+) and proton affinities[PA=(EBH+-EB), hartree] at the equilibrium geometry of the ground state.

Molecule	Total Energy(hartree)		Proton Affinity(hartree)
	B	BH^+	
ACR, X = -H	-247.3692	-247.7160	-0.3468
βMACR, X = $-CH_3$	-286.6979	-287.0491	-0.3512
βMyACR, X = $-OCH_3$	-361.7297	-361.9961	-0.2664
βAACR, X = $-NH_2$	-302.7594	-303.1248	-0.3654
βClACR, X = -Cl	-706.9850	-707.3301	-0.3451
βCnACR, X = -CN	-339.6279	-339.9596	-0.3317
βNACR, X = $-NO_2$	-451.9159	-452.2472	-0.3313

Table 2

Computed net charge on O-atom (q_O-) of free base (B) and O-protonated base (BH^+) and computed net charge on proton (q_{H^+}) at the equilibrium ground state of protonated base (BH^+) and free base (B)

Molecule	Charge on Carbonyl Oxygen atom(q_{O^-})		Charge on Proton(q_{H^+})
	B	BH^+	
ACR, X = -H	-0.3637	-0.2457	0.3059
βMACR, X = $-CH_3$	-0.3757	-0.2710	0.2951
βMyACR, X = $-OCH_3$	-0.3897	-0.2817	0.3651
βAACR, X = $-NH_2$	-0.4432	-0.3436	0.2963
βClACR, X = -Cl	-0.3429	-0.2316	0.2864
βCnACR, X = -CN	-0.3319	-0.2471	0.3091
βNACR, X = $-NO_2$	-0.3449	-0.2386	0.3070

Table 3

Geometrical features of the free base and O-protonated base (length in Å and angle in degree).

Molecule	Free base	O-protonated base			
	r(C–O)	r(C–O)	r(O–H$^+$)	<C–O–H$^+$	<C–C–O–H$^+$
ACR, X = -H	1.2183	1.3057	0.9679	113.2913	-5.4293
βMACR, X = -CH_3	1.2219	1.3105	0.9690	114.6336	180.0044
βMyACR, X = -OCH_3	1.2232	1.2232	1.4448	102.8165	-174.3517
βAACR, X = -NH_2	1.2375	1.3328	0.9669	114.1474	-179.4498
βClACR, X = -Cl	1.2155	1.3017	0.9770	112.3551	-0.0481
βCnACR, X = -CN	1.2152	1.3008	0.9703	116.1180	179.9410
βNACR, X = -NO_2	1.2188	1.3071	0.9708	115.1478	-179.9838

Table 4

Computed hardness (hartree) and softness (hartree) of the free base (B) in the ground state by B3LYP(DFT) method using 6-311G(d,p) basis set.

Molecule	$\in_{HOMO}$	$\in_{LUMO}$	η (Hardness)	S = 1/2η (Softness)
ACR, X = -H	-0.2585	-0.0410	0.1087	4.5998
βMACR, X = -CH_3	-0.2509	-0.0341	0.1084	4.6125
βMyACR, X = -OCH_3	-0.2205	-0.0533	0.0836	5.9808
βAACR, X = -NH_2	-0.2118	-0.0079	0.1019	4.9067
βClACR, X = -Cl	-0.2587	-0.0537	0.1025	4.8780
βCnACR, X = -CN	-0.2756	-0.0910	0.0923	5.4171
βNACR, X = -NO_2	-0.2829	-0.1244	0.0792	6.3131

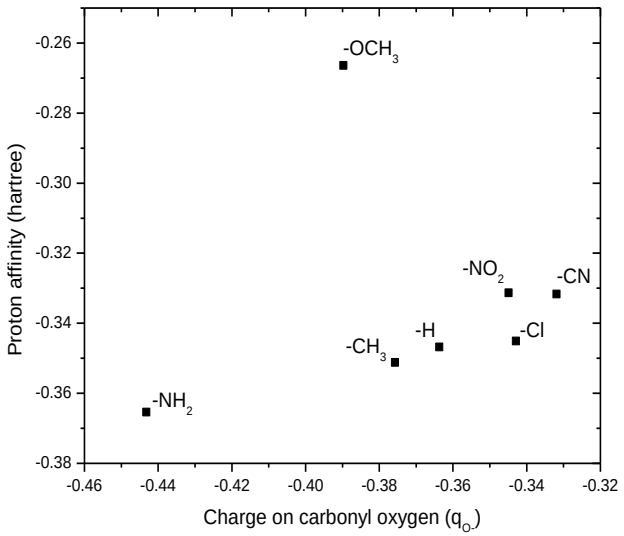


Figure 1

Lot of gas phase ground state proton affinity vs. charge on the carbonyl oxygen atom of the free bases.

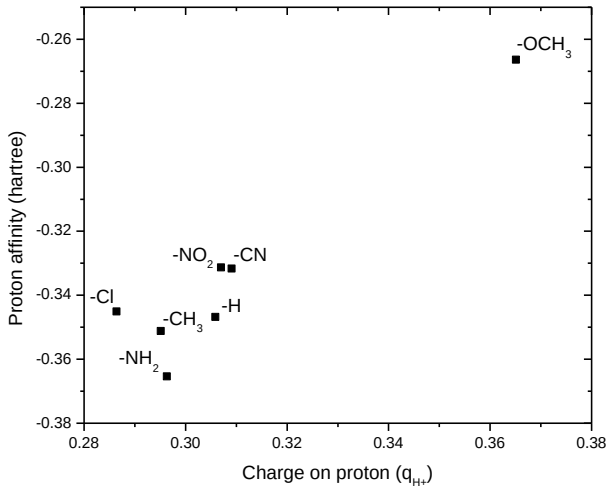


Figure 2

Plot of gas phase ground state proton affinity vs. charge on the proton of the complex BH+

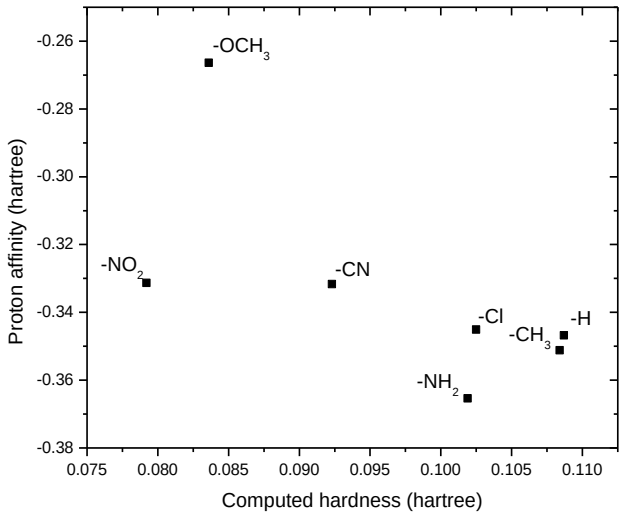
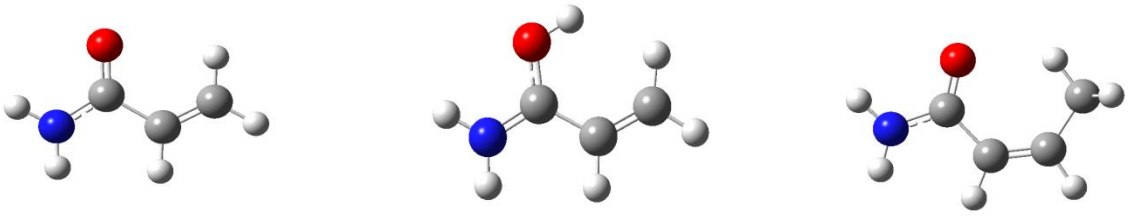
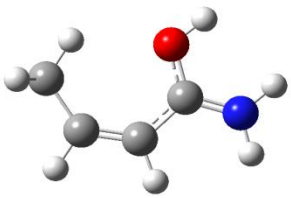


Figure 3

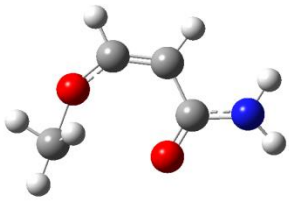
Plot of gas phase ground state proton affinity vs. computed hardness.



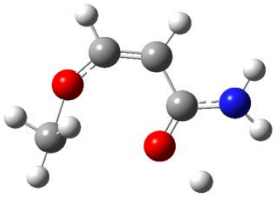
ACR ACR(H^+) βMACR



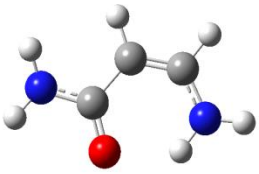
βMACR(H^+)



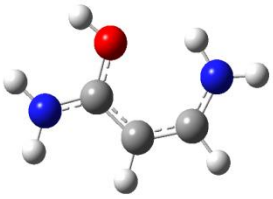
βMyACR



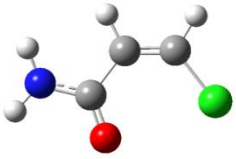
βMyACR(H^+)



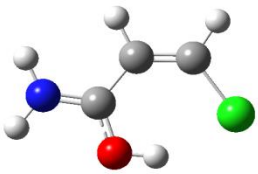
βAACR



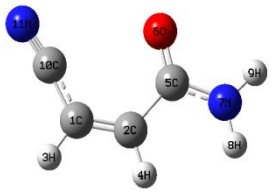
βAACR(H^+)



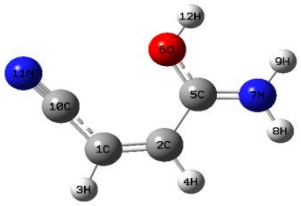
βClACR



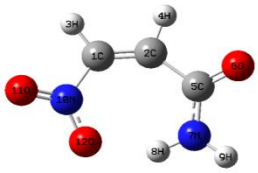
βClACR(H^+)



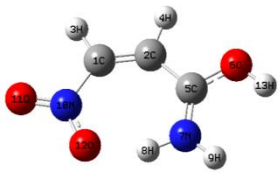
βCnACR



βCnACR(H^+)



βNACR



βNACR(H^+)

Figure 4

Optimized structure of β-substituted acrylamides and their O-protonated counterparts in the ground state.

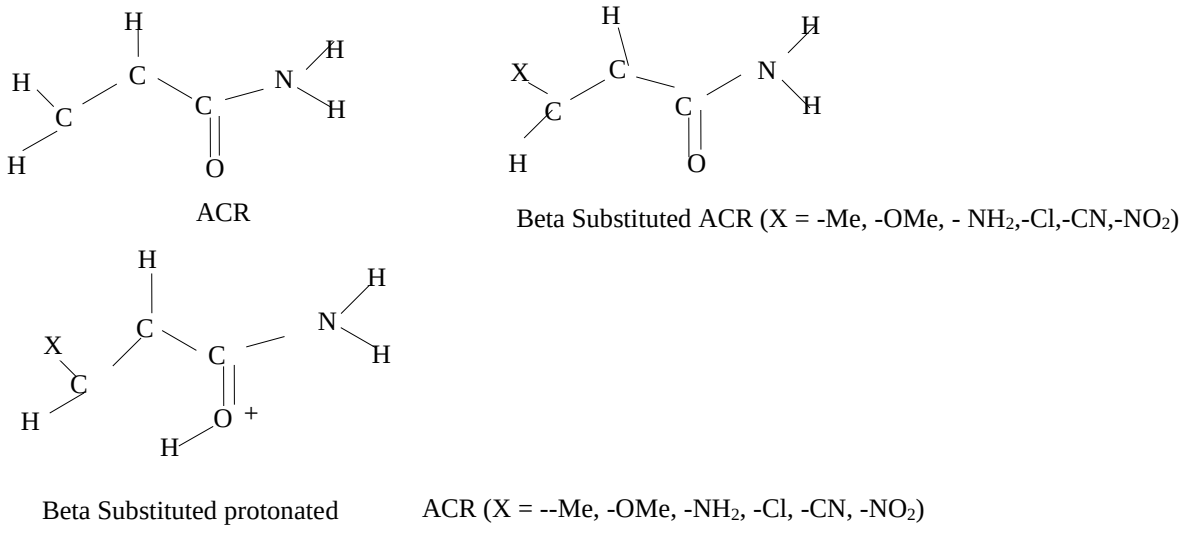


Figure 5
Structure of ACR, Beta Subtituted ACR and their Protonated Counterparts

4. CONCLUSION

The above computational study shows that gas phase O-protonation of β-substituted acrylamides and their O-protonated counterparts is spontaneous irrespective of their electron releasing or withdrawing nature. The overall proton affinity is explained by distant atom contribution in addition to the contribution from the carbonyl group. The carbonyl ring near invariant stereochemistry around the protonation site of each base tends to suggest that the entire contribution from substituent effects to PA cannot be modelled properly unless contributions from far away centres are taken into account.

Acknowledgment
Authors expressed big gratitude to the Prof. B.R. DE for his kind co-operation to complete this work and also grateful to the Department of Chemistry and Chemical technology, Vidyasagar University, Medinipur, West Bengal, India, for providing all the facilities for doing research works in this area. A lot of thanks to other researchers for their important comment in various circumstances for this work.

Peer-review
External peer-review was done through double-blind method.

Funding
This study has not received any external funding.

Conflict of Interest
The authors declare that there are no conflicts of interests.

Data and materials availability
All data associated with this study are present in the paper.

REFERENCES & NOTES

1. Bhome DK, Hemsworth RS, Rundle HI, Schiff, HI. *J. Chem. Phys.* 1973, 58, 3504.
2. Beauchamp JL, "Interaction between Ions and Molecules", (Plenum, New York) 1974, 413, 459, 489.
3. Yamadagni R, Kebarle PJ. *J. Am. Chem. Soc.* 1973, 96, 727.
4. Bhome DK, Mackay GI, Schiff HI, Hemsworth RS. *J. Chem. Phys.* 1974, 61, 2175.

5. Solomon JJ, Meot MN, Field FM. *J. Am. Chem. Soc*. 1974, 96, 3727.
6. Long JI, Franklin JL. *J. Am. Chem. Soc*. 1974, 96, 2320.
7. Brauman JI, Blair LK. *J. Am. Chem. Soc*. 1970, 92, 5986.
8. Wieting RD, Staley RH, Beacchamp JL. *J. Am. Chem. Soc*. 1974, 96, 7552.
9. Staley RH, Beacchamp JL. *J. Am. Chem. Soc*. 1975, 96, 3727.
10. Pandit S, De D, De BR. *J. Mol. Struct*. (*Theochem*). 2006, 760, 245-246.
11. Senapati U, De D, De BR. *Indian J. Chem*. 2008, 47A, 548-550.
12. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, Montgomery JA. Jr, Vreven T, Kudin KN, Burant JC, Millam JM, Iyengar SS, Tomasi J, Barone V, Mennucci B, Cossi M, Scalmani G, Rega N, Petersson GA, Nakatsuji H, Hada M, Ehara M, Toyota K, Fukuda R, Hasegawa J, Ishida M, Nakajima T, Honda Y, Kitao O, Nakai H, Klene M, Li X, Knox JE, Hratchia HP, Cross JB, Adamo C, Jaramillo J, Gomperts R, Stratmann RE, Yazyev O, Austin AJ, Cammi R, Pomelli C, Ochterski JW, Ayala PY, Morokuma K, Voth GA, Salvador P, Dannenberg JJ, Zakrzewski VG, Dapprich S, Daniels AD, Strain MC, Farkas O, Malick DK, Rabuck AD, Raghavachari K, Foresman JB, Ortiz JV, Cui Q, Baboul AG, Clifford S, Cioslowski J, Stefanov BB, Liu G, Liashenko A, Piskorz P, Komaromi I, Martin RL, Fox DJ, Keith T, Al-Laham MA, Peng CY, Nanayakkara A, Challacombe M, Gill PMW, Johnson B, Chen W, Wong MW, Gonzalez C, Pople JA, Gaussian, Inc, *Wallingford*, CT, 2004.
13. Lee C, Yang W, Parr RG. *Phys. Rev*.1988, B37, 785; Becke AD. *J. Chem. Phys*. 1993, 98, 5648.