Electrophilicity-Based Charge Transfer Descriptor

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In line with the charge transfer ($\Delta N_{max} = -\mu/\eta$) proposed by Parr et al. (Parr, R. G.; Szentpály, L. V.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922), we propose an electrophilicity-based charge transfer (ECT) descriptor in this paper and validate it through the interaction between a series of chlorophenols and DNA bases. Application of ECT can be extended to the interaction of any toxin with the biosystem.

Introduction

In the field of drug design, and protein and DNA functioning, the ligand-binding phenomenon plays a crucial role. Although several types of interactions are involved in such a process, in scores of cases, partial charge transfer through covalent bonding, dative bonding, or hydrogen bonding takes place.[1] Maynard et al. have made a qualitative suggestion that electronegativity squared divided by hardness measures the electrophilic power of a ligand, its propensity to soak up electrons, and is used in understanding the reactivity of the human immunodeficiency virus type 1 (HIV− 1) nucleocapsid protein p7 (NCp7) when reacted with a variety of electrophilic agents.[2]

Parr et al. have introduced a global electrophilicity index ω in eq 1

$$\omega = \frac{\mu^2}{2\eta} \tag{1}$$

where μ and η are the chemical potential and chemical hardness, respectively, defined elsewhere.[3,4]

The global interactions between the constituents of chlorophenols (CPs) and DNA bases have been determined using the parameter ΔN, which represents the fractional number of electrons, transferred from system A to system B, and is represented by[5]

$$\Delta N = \frac{\mu_B - \mu_A}{2(\eta_A + \eta_B)} \tag{2}$$

where μ_A, μ_B and η_A, η_B are the chemical potentials and chemical hardnesses of systems A and B, respectively. If $\Delta N < 0$, charge flows from A to B (A acts as electron donor), and if $\Delta N > 0$, charge flows from B to A (A acts as electron acceptor). Our earlier studies[6−9] have shown the importance of ΔN in the charge transfer analysis and also the usefulness of other descriptors in the analysis on the interaction of toxins with the biosystems.

Electrophilicity-Based Charge Transfer (ECT) Descriptor. Associated with the definition of global electrophilicity, there is an additional and useful relationship that accounts for the maximum electronic charge ΔN_{max} that the electrophile may accept from the environment. Here, the environment may be represented by either external effects coming, for instance, from the interaction with the solvent or more simply as field effects coming from the presence of substituent groups in the molecule. ΔN_{max} has been defined as[1]

$$\Delta N_{max} = -\mu/\eta \tag{3}$$

Electrophilicity of a system can be written in terms of ΔN_{max} as follows:

$$\omega = \mu^2/2\eta = (-\mu/2)(-\mu/\eta) = \chi\Delta N_{max}/2 \tag{4}$$

where χ is the electronegativity of the system.

Hence

$$\Delta N_{max} = 2\omega/\chi = 2\omega X \tag{5}$$

where $X = 1/\chi$.

If we consider the two systems A and B approaching each other, the amount of charge transfer between them can be written in terms of electrophilicity, that is, electrophilicity-based charge transfer (ECT) can be written as

$$\mathrm{ECT} = (\Delta N_{max})_A - (\Delta N_{max})_B = 2[\omega_A X_A - \omega_B X_B] \tag{6}$$

If ECT < 0, charge flows from A to B (A acts as an electron donor) and if ECT > 0, charge flows from B to A (A acts as electron acceptor). It is tacitly assumed that the electrophilicity effect dominates the electronegativity effect.

Results and Discussion

The geometries optimized at the B3LYP/6-31G* level[10−12] using the Gaussian 98W suite of programs,[13] and the calculated values of hardness (η), chemical potential (μ), electrophilicity index (ω), and the charge transfer (ΔN) of the selected 19 chlorophenols and DNA bases are taken from our previous study.[9]

The chemical potential, chemical hardness, and electrophilicity index for the chlorophenols and DNA bases viz., adenine (A), guanine (G), thymine (T), and cytosine (C), are presented in Table 1. If the two systems X and Y are brought together, as in a reaction they must form a single system with constant values of chemical potential. The negative chemical potential can be

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TABLE 1: Global Reactivity Descriptors for the Selected Systems from the B3LYP/6-31G* Method[a]

molecule[b]	μ	η	ω
2-MCP	−0.1213	0.1083	0.0680
3-MCP	−0.1223	0.1087	0.0688
4-MCP	−0.1193	0.1045	0.0681
2,3-DCP	−0.1314	0.1068	0.0808
2,4-DCP	−0.1306	0.1028	0.0829
2,5-DCP	−0.1330	0.1063	0.0832
2,6-DCP	−0.1318	0.1065	0.0815
3,4-DCP	−0.1293	0.1034	0.0808
3,5-DCP	−0.1352	0.1084	0.0843
2,3,4-TCP	−0.1376	0.1015	0.0932
2,3,5-TCP	−0.1425	0.1057	0.0962
2,3,6-TCP	−0.1396	0.1038	0.0939
2,4,5-TCP	−0.1394	0.1015	0.0957
2,4,6-TCP	−0.1400	0.1013	0.0967
3,4,5-TCP	−0.1387	0.1026	0.0938
2,3,4,5-TTP	−0.1460	0.1005	0.1061
2,3,4,6-TTP	−0.1458	0.0995	0.1068
2,3,5,6-TTP	−0.1484	0.1033	0.1066
PCP	−0.1518	0.0987	0.1167
adenine	−0.1140	0.1047	0.0621
thymine	−0.1356	0.1064	0.0864
guanine	−0.0973	0.1072	0.0442
cytosine	−0.1238	0.1023	0.0750

[a] Data from our previous study: ref 9. All data are in au. [b] MCP, monochlorophenol; DCP, dichlorophenol; TCP, trichlorophenol; TTP, tetrachlorophenol; and PCP, pentachlorophenol.

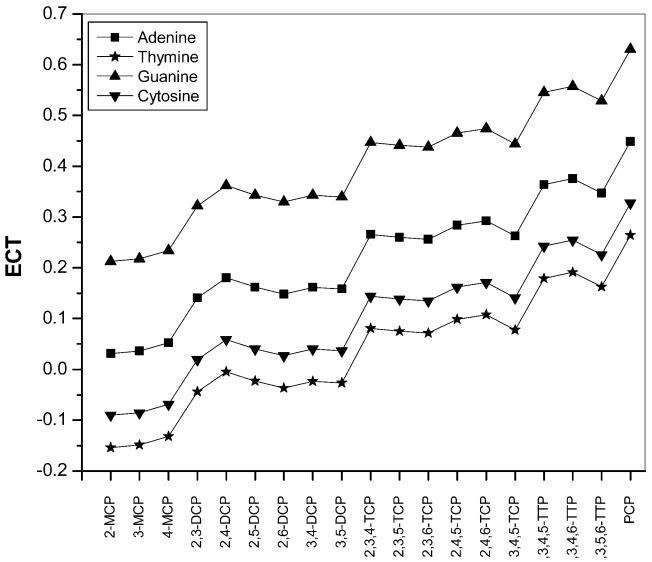

Figure 1. Charge transfer between chlorophenols and DNA bases based on ECT from the B3LYP/6-31G* method.

called the absolute electronegativity, and there is always a transfer of electrons from a less electronegative system to a more electronegative system. The amount of charge transfer between CPs and various nucleic acid bases is calculated based on ΔN and ECT methods to know about the possible interaction of CPs with the biosystems (Table 2). Positive values of both ΔN and ECT in Table 2 indicate that the respective CPs act as electron acceptors, and the corresponding negative values indicate that the respective CPs act as electron donors.

In the case of the interaction of CPs with adenine, both ΔN and ECT methods yielded only positive values, indicating the fact that all selected CPs act as electron acceptors. One may note that there is an increased amount of electron transfer from adenine to CPs as predicted by the ECT method as compared to the ΔN method. Both methods show that the largest amount of charge transfer takes place with respect to PCP. Mono- and

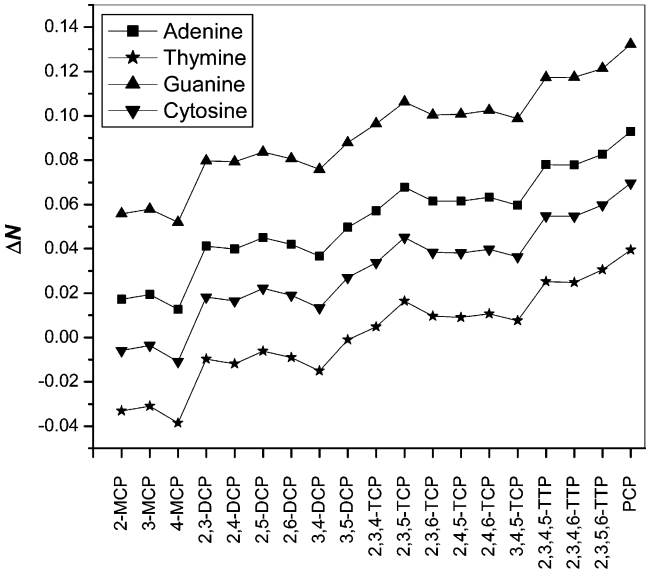

Figure 2. Variation of charge transfer between chlorophenols and DNA bases based on ΔN from the B3LYP/6-31G* method.

dichlorophenols act as electron donors, while all other CPs act as electron acceptors during their interaction with thymine.

For guanine interaction with CPs, the flow of electrons is from guanine to CPs, indicating CPs to be good electron acceptors. During the interaction of CPs with cytosine, mono-CPs act as electron donors while all other selected CPs act as electron acceptors. This shows that the ECT method like ΔN is capable of identifying the nature of charge transfer in a transparent manner.

The amount of charge transfer taking place during the interaction of CPs with DNA bases as obtained using the ECT method is presented in Figure 1. The maximum amount of charge transfer takes place between CPs and guanine, whereas the minimum amount of charge flows between CPs and thymine similar to that obtained using ΔN (Figure 2).[9] The new ECT depends on $(\chi_A/\eta_A - \chi_B/\eta_B)$ as opposed to $(\chi_A/(\eta_A + \eta_B) - \chi_B/(\eta_A + \eta_B))$ as in eq 2. The former appears to be more appropriate because it takes care of individual propensity and resistance of charge transfer. Although the direction of the electron transfer will depend on the electronegativity difference $(\chi_A - \chi_B)$, the amount of the electron transfer would depend on both $(\chi_A - \chi_B)$ and $(\eta_A + \eta_B)$, or in the new ECT definition the difference between respective (χ/η) values but for the rare cases where $(\chi_A - \chi_B)$ may have an opposite sign than that of $(\chi_A/\eta_A - \chi_B/\eta_B)$, where even the direction of the electron flow would be altered. Apart from the electronegativity aspects, electron transfer will also depend on respective polarizability (softness) values. Comparison of the ECT with the amount of CT obtained from the ΔN in two interacting systems has been made. Figure 3 depicts a reasonably good correlation between CT obtained through ECT and ΔN methods, between two interacting systems. The previous discussion based on ECT provides a clear picture about the nature of the interaction of CPs with the biosystems and hence can be utilized as a tool in analyzing the charge transfer between any selected toxin and biosystems. It may be used in molecular electronics as well.[14]

Conclusion

An electrophilicity-based charge transfer (ECT) descriptor has been proposed in this work. It has been successfully tested on

TABLE 2: Charge Transfer between Chlorophenols and DNA Bases Based on ΔN and ECT Methods

	ΔN[a]				ECT[b]			
molecule[c]	Adenine	thymine	guanine	cytosine	adenine	thymine	guanine	cytosine
2-MCP	0.0172	−0.0332	0.0558	−0.0059	0.0311	−0.1539	0.2125	−0.0903
3-MCP	0.0194	−0.0310	0.0579	−0.0036	0.0362	−0.1488	0.2176	−0.0853
4-MCP	0.0127	−0.0386	0.0520	−0.0109	0.0528	−0.1322	0.2341	−0.0687
2,3-DCP	0.0412	−0.0098	0.0797	0.0182	0.1409	−0.0441	0.3223	0.0195
2,4-DCP	0.0399	−0.0120	0.0792	0.0165	0.1804	−0.0045	0.3618	0.0590
2,5-DCP	0.0450	−0.0061	0.0836	0.0221	0.1619	−0.0231	0.3433	0.0405
2,6-DCP	0.0420	−0.0090	0.0806	0.0190	0.1482	−0.0367	0.3296	0.0268
3,4-DCP	0.0367	−0.0151	0.0759	0.0133	0.1616	−0.0234	0.3430	0.0401
3,5-DCP	0.0497	−0.0010	0.0878	0.0270	0.1583	−0.0267	0.3397	0.0369
2,3,4-TCP	0.0571	0.0047	0.0964	0.0338	0.2657	0.0807	0.4471	0.1443
2,3,5-TCP	0.0678	0.0164	0.1063	0.0451	0.2600	0.0750	0.4414	0.1385
2,3,6-TCP	0.0615	0.0096	0.1003	0.0384	0.2563	0.0713	0.4377	0.1348
2,4,5-TCP	0.0615	0.0090	0.1007	0.0382	0.2838	0.0988	0.4652	0.1623
2,4,6-TCP	0.0632	0.0107	0.1024	0.0398	0.2926	0.1076	0.4740	0.1711
3,4,5-TCP	0.0596	0.0075	0.0987	0.0364	0.2627	0.0777	0.4440	0.1412
2,3,4,5-TTP	0.0780	0.0252	0.1173	0.0548	0.3641	0.1791	0.5454	0.2426
2,3,4,6-TTP	0.0779	0.0248	0.1174	0.0546	0.3760	0.1910	0.5574	0.2545
2,3,5,6-TTP	0.0826	0.0305	0.1213	0.0598	0.3474	0.1624	0.5288	0.2259
PCP	0.0929	0.0395	0.1323	0.0696	0.4491	0.2641	0.6304	0.3276

[a] Data from our previous study: ref 9. [b] Present study. All data are in au. [c] MCP, monochlorophenol; DCP, dichlorophenol; TCP, trichlorophenol; TTP, tetrachlorophenol; and PCP, pentachlorophenol.

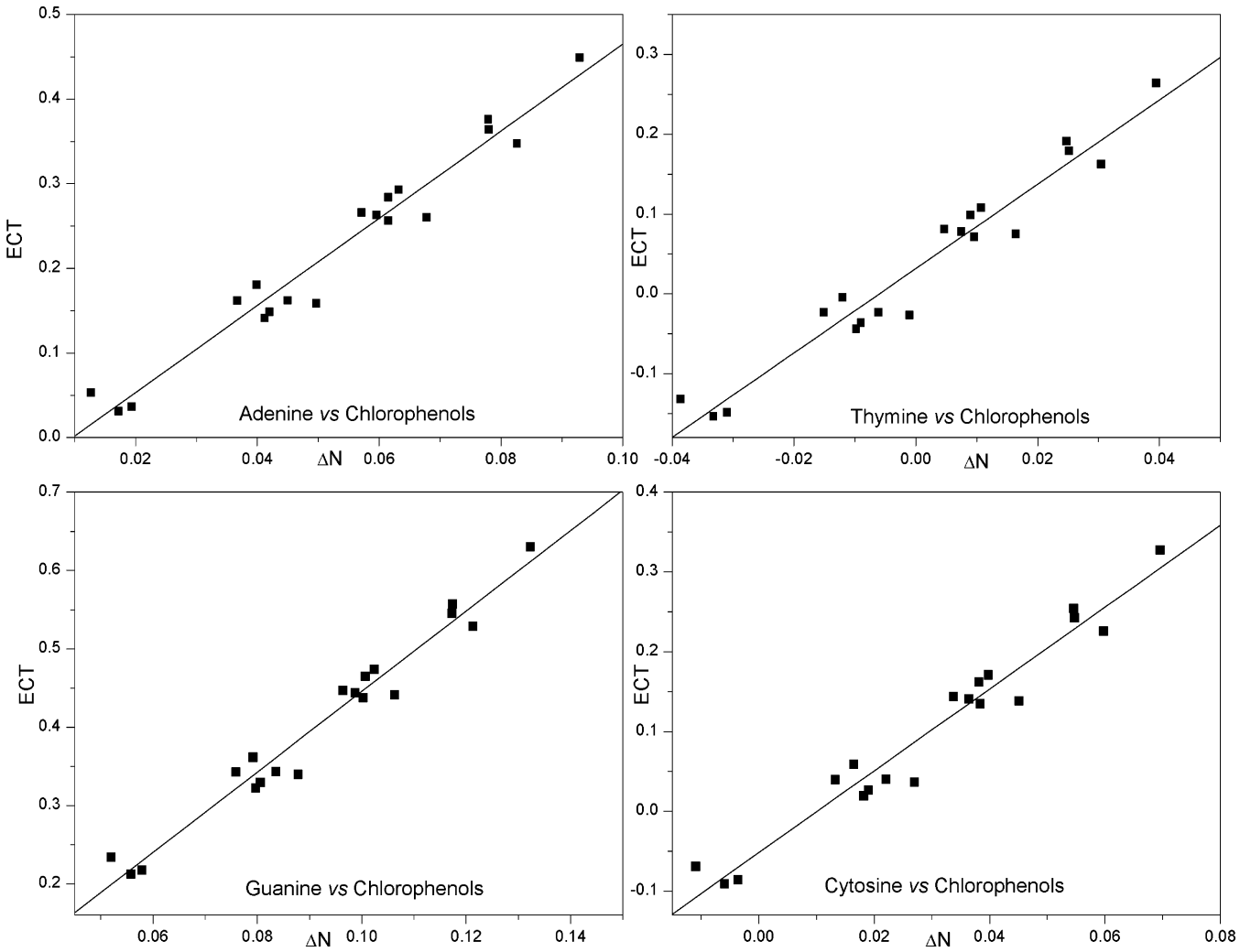

Figure 3. Comparison of the ECT with the amount of CT obtained from ΔN in the two interacting systems.

the interaction between a series of chlorophenols and DNA bases. ECT shows that the maximum amount of charge transfer takes place between CPs and guanine, whereas the minimum amount of charge flows between CPs and thymine. Hence, one can conclude that the charge transfer between any selected toxin and biosystem can be analyzed using ECT as a descriptor.

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