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A DFT Study on the Polarizability of Di-substituted Arene (*o*-, *m*-, *p*-) Molecules used as Supercharging Reagents during Electrospray Ionization Mass Spectrometry

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Abstract : During electrospray ionization mass spectrometry (ESI-MS) analysis of proteins, the addition of supercharging agents allows for adjusting the maximal charge state, affecting the charge state distribution, and increases the number of ions reaching the detector thus, improving signal detection. We postulate that in di-substituted arene isomers, molecules with higher polarizability values should generate greater interactions and hence elicit higher signal intensities. Polarizability is an electronic parameter which has been demonstrated to predict many chemical interactions. Many properties can be predicted based on charge polarization. Molecular polarizability is a vital descriptor for explaining intermolecular interactions. We employed DFT (density functional/Hartree-Fock hybrid model, B3LYP)-derived descriptors and computed molecular polarizability for ten di-substituted arene reagents, each set made up of three (*ortho, meta, para*) isomers, with reported use as supercharging reagents during ESI experiments. The atomic electronic inputs were ionization potential (IP), electron affinity (EA), electronegativity (χ), hardness (η), chemical potential (μ), and dipole moment (D). We determined that the *para* isomers showed the highest polarizability values in nine of the ten sets. There was no difference between the *ortho* and *meta* isomers. Polarizability also increased with increasing complexity of the substituents on the benzene ring. Polarizability correlated positively with IP, EA, χ, η, and D but correlated negatively with chemical potential. This DFT study predicts that the *para* isomers of di-substituted arene isomers should elicit the strongest ESI responses. An experimental comparison of the three isomers, especially of larger supercharging molecules, could be carried out to establish this premise.

Key words : Polarizability, supercharging reagents, electrospray ionization, gas-phase, DFT

Introduction

Supercharging reagents

In ESI-MS, one of the main approaches for increasing the generation and detection of higher charge state in protein ions (i.e., from $[M+nH]^{n+}$ to $[M+(n+1)H]^{n+1}$) and, simultaneously improving the signal intensity (ESI response) is the addition of small amounts (approx. < 5% *v/v* of the mobile phase solution) of charge-inducing compounds or supercharging reagents.[1,2] Often used supercharging reagents include *m*-nitrobenzyl alcohol (3-nitro(phenyl) methanol), *o*-nitrobenzyl alcohol (2- nitro(phenyl)methanol), and sulfolane. In previous work, we evaluated a comprehensive list of 34 supercharging reagents that have been used in experiments (between 2000 to 2021), and we included an additional 19 potential candidate isomers.[3]

Thus far, the supercharging reagents used in experiments are all small molecules (MW < 180 Da), many are di-substituted arene molecules, and typically, they are readily ionized as all have proton donating or accepting substituent groups.

Some of the physico-chemical properties that have been shown or deduced to confer such charge-enhancing and improved signal intensity attributes are the colligative properties: boiling points, surface tension, acidity/basicity, dipole moments, and polarizability. All the supercharging reagents have higher boiling points compared with typical aqueous/organic solvents used in ESI. Therefore, they are

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less volatile and can raise the surface tension of the electrospray solution.[4] The reagents also generally have higher dipole moments compared with the solvents used, except for acetonitrile.[5] For example, the most effective supercharging reagents have one or more carbonyl, sulfonyl, or nitro groups present in their molecular structure, which would be necessary for intermolecular interactions between the supercharger and analytes, e.g. proteins. Furthermore, supercharging reagents exhibit low solution-phase basicities and relatively low gas-phase basicities compared with the solvents.[6,7]

There are some other interactions between supercharging reagents and proteins, especially when supercharging reagents are added at concentrations approximately equal to the concentration of the protein under investigation. Prominent among these interactions are adduct formation [5,8,9] and chemical denaturation.[8] It should be noted that all these different supercharging properties have been proposed to influence their performance, but not all of them are relevant at any one time. Experimental conditions increase the prominence of one or several of them over the other properties depending on the aims of the study. Since, many of the supercharging reagents are di-substituted arene molecules, here, using theoretical calculations, we consider the role of polarizability as a possible descriptor of arene supercharging reagents.

Polarizability and dipole moments

For clarity, we re-state the two related terms: the dipole moment and polarizability. The electric dipole moment is a measure of the separation of positive and negative electrical charges within a system, matter, molecule or charged entity, that is, a measure of the overall polarity of the system. The SI unit for electric dipole moment is the coulomb-meter (C·m). The debye (D) is another unit of measurement which is frequently used. An ideal dipole consists of two opposite charges with infinitesimal separation.

Polarizability refers to the tendency of matter, molecule or charged particle when subjected to an electric field to acquire an electric dipole moment in proportion to that applied field. It is a property of all matter, made up of elementary particles which have an electric charge due to their protons and electrons. Under an electric field, the negatively charged electrons and positively charged atomic nuclei are subject to opposite forces and undergo charge separation. Polarizability is responsible for the dielectric constant of a material and, at high (optical) frequencies, its refractive index. Thus, polarizability of a molecule, **α**, is defined as the constant of proportionality between the strength of an applied electric field, **ε**, and the magnitude of the electric dipole moment the field induces.

Thus,

$$\mu_{induced} = \alpha\varepsilon \quad (1)$$

Polarizability has the SI units of $C{\cdot}m^2{\cdot}V^{-1} = A^2{\cdot}s^4{\cdot}kg^{-1}$ while its cgs unit is cm^3. Usually, it is expressed in cgs units as a so-called polarizability volume, sometimes expressed in $Å^3 = 10^{-24}\ cm^3$. Technically, polarizability is a tensor quantity, i.e., having the attributes of a stress or a strain, which has magnitude, direction, and a plane in which it acts. However, for spherically symmetric charge distributions, it reduces to a single number. In many cases, an average polarizability is usually adequate in calculations. Polarizability is therefore greatly influenced by the electronic properties of atoms or molecules.

The role of polarizability

Many properties can be predicted based on charge polarization. These properties include boiling and melting points, vaporization and fusion enthalpies, Trouton constants, solubility parameters, polarity solvent scales, and the structural properties of liquids.[10] Polarizability has been extensively applied in drug design, particularly in quantitative structure property relationship (QSPR) and quantitative structure-activity relationship (QSAR) studies. For instance, that polarizability is correlated with the logarithm of the n-octanol/water partition coefficient, log P,[11] and the square of the correlation coefficient ($\rho 2$) between polarizability and aqueous solubility.[12] The property of polarizability has successfully been applied in constructing QSPR models for many molecular properties, including aqueous solubility,[13] Henry's law constant,[14] the partition coefficient of vaporous chemicals in a water-gas phase[15] and vapor pressure[16] and many others.

Polarizability has been established as an essential factor in determining chemical reactivity.[17] Molecular polarizability is a vital descriptor to explain intermolecular interactions, and ligand-substrate interactions and is a promising descriptor to study chemical-biological interactions.[18]

Experimental determination of polarizability

Most empirical models are based on a hypothesis that molecular polarizability is additive. Polarizability of a molecule can be determined by the sum of the contributions of atoms and/or functional groups in the molecule. Therefore, experimentally, polarizability can be determined from the values of the refractive index (0.5% or higher) and density of the molecule using the Lorentz-Lorentz equation that relates **α** to the molar refraction, ***R***. Therefore,

$$R = [(n_D^2 - 1)/(n_D^2 + 2)]\frac{M}{\rho} = \frac{4}{3}\pi N_0 \alpha \quad (2)$$

Where n_D is the refractive index at the sodium *D*-line (589 nm wavelength), the quotient between the molecular weight, *M*, and the density, ρ, is the molar volume, *V*, of the molecule, and N_0 is the Avogadro constant. According to the Lorentz-Lorentz equation, the relationship between the polarizability, **α,** and the molar refraction, ***R***, is α = 0.3964

R, where *R* is expressed in mL and α in Å^3. Other experimental methods allow the determination of the polarizability from measures of magnitudes, such as from dipole moments or dielectric constants.

Computational determination of polarizability

Quantum mechanical calculation of molecular polarizability can be carried out by solving the coupled perturbed Hartree-Fock (CPHF) equations with electric field perturbations.[12] Verma *et al.*[19] simply calculated polarizability by adding up the number of valence electrons. While others determined the polarizability of 426 compounds, mainly solvents, from the atomic composition of the molecules only.[20] Brief reviews of some fast empirical approaches for estimating static molecular polarizabilities are given.[12,18]

Our primary focus in this study is on the property of polarizability of di-substituted arene molecules which have been or may be used as supercharging reagents.[3] We work on the established fact that, if polarizability greatly influences many intermolecular interactions, leading to it being used to predict, for example, QSAR, aqueous solubility, etc., then, here we explore through theoretical calculations, the possibility that, it could well predict interactions between analytes (proteins) and supercharging reagents which are di-substituted arene molecules. The isomer with the highest polarization value would likely generate a greater interaction with the protein, and hence a higher ESI signal intensity. We aimed to address a specific question: In di-substituted arene isomers with 6-membered aromatic ring structure with two substituents, the first at the *ipso* (C-1) position and the second at either *ortho* (C-2), *meta* (C-3) or *para* (C-4) position, which stereoisomer is most polarizable and how would they rank? We assume all factors governing the ESI-MS environment and supercharging are held constant. Thus, analyte: composition and concentration; mobile phase: composition, pH, flow rate; mass spectrometer instrument settings: voltages, nebulizer gas, gas flow etc. are all held constant, and the only variable is the three di-substituted arene supercharging reagents being compared at the same concentration. Examples of these isomers are 2-nitrochlorobenzene, 3-nitrochlorobenzene, and 4 nitrochlorobenzene (Figure 1).

Experimental

Data source

Our data source is primarily taken from Abaye *et al.*[3] The computation used was accessed from the Centre for High Performance Computing, CSIR, Pretoria, South Africa.

Model Construction

The molecules under study are in the gas phase. The optimized compounds consist of ten sets of di-substituted arene isomers. Each set consists of three isomers with the same substituent differencing in its position, i.e., 2- (*ortho*), 3- (*meta*), or 4- (*para*). Thus, a total of 30 compounds were evaluated (Table 1).

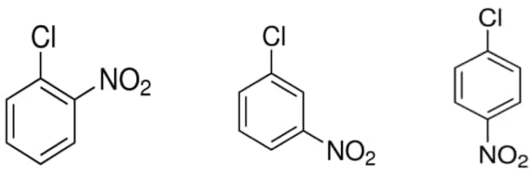

Figure 1. The isomers of nitrochlorobenzene: *ortho* (C-2), *meta* (C-3), or *para* (C-4) position, respectively. The Cl atom is at the *ipso* (C-1) position.

Computation

We applied the density functional/Hartree-Fock hybrid model, B3LYP[21-24] in computing molecular polarizability of the selected di-substituted arene supercharging reagents to explore its potential in determining which of the three di-substituted arene isomer has the highest polarizability value and if a ranking could be developed. It is anticipated that the isomer with the highest polarizability value would be better able to interact with the protein molecule and thus generate the greatest ESI response under the same experimental conditions. For this purpose, the activities of the supercharging reagents have been modelled, in the gas-phase, using the atomic property of additivity with the following electronic inputs: ionization potential (IP), electron affinity (EA), electronegativity (χ), hardness (η), chemical potential (μ) and dipole (D) (Table 1).

The atomic values were determined from the following equations:[25]

$$IP = -E^{HOMO} \tag{3}$$

$$EA = -E^{LUMO} \tag{4}$$

$$\chi = -\frac{1}{2}(E^{HOMO} + E^{LUMO}) \tag{5}$$

$$\mu = \frac{1}{2}(E^{HOMO} + E^{LUMO}) \tag{6}$$

$$\eta = \frac{1}{2}(E^{HOMO} - E^{LUMO}) \tag{7}$$

Where E^{HOMO} and E^{LUMO} are the energies of the highest occupied molecular orbital and lowest unoccupied molecular orbital, associated with these atomic properties for each element in the compounds under investigation.

Calculations employed the density functional/Hartree-Fock hybrid model, B3LYP and the 6-311++G (2df, 2p) basis set[26] as implemented in the Gaussian 09 program.[27] All structural optimizations were done without symmetry restrictions. All optimized structures were subjected to

normal mode analysis to verify the nature of the stationary points located. The geometries of several supercharging compounds were optimized as either the neutral or the anion species at the B3LYP/6-311++G(2df, 2p) to obtain the values of ionization potential (IP), electron affinity (EA), electronegativity (χ), hardness (η), chemical potential (μ), dipole moment (D) and polarizability (α).

Results and discussion

Evidence of the critical role of peptides and proteins in pathophysiology in now available in abundance, and there is a pressing need for the development of highly sensitive bioanalytical methods, including ESI-MS. Integral to the ESI analysis of peptides and proteins is the production of multiple charge states, which sometimes confound and interfere with sensitive method development. Supercharging reagents allow modifying the maximal charge state and the corresponding distribution of charges, potentially increasing the number of ions reaching the mass spectrometer detector and thus, improving signal detection. Of the supercharging reagents used in ESI experiments, many are di-substituted arene molecules.

We set out to compute the polarizability values in di-substituted arene molecules which are used as supercharging reagents. This was achieved by employing the density functional/Hartree-Fock hybrid model, B3LYP. It is anticipated that the determined polarizability values would have a ranking among the (*ortho* (2)-, *meta* (3)- and *para* (4)- di-substituted arene) isomers. Here, we assume that all other factors influencing ESI-MS and supercharging are held constant. Thus, the ranking would serve as a possible descriptor of their ability to elicit enhanced ESI responses.

Examination of Table 1 shows that the *para* isomer consistently had the highest polarizability values of the ten sets of compounds, except for the first set (1-3). There was no clear trend between the *ortho* and *meta* isomers. This observation is entirely reflected in simple di-substituted arenes where the three isomers tend to have rather similar boiling points. However, the *para* isomer usually has the highest melting point (Table 1) and the lowest solubility in a given solvent of the three isomers. Secondly, the molecules bearing more complex substituents have higher polarizability values. For example, the chlorophenols (1-3) and nitrochlorobenzenes (4-6), two of the simplest molecular structures have relatively lower polarizability values than the nitrophenylethanols (16-18) or nitrophenethyl alcohols (22-24), whose substituents are more complex.

Having empirically computed the DFT-derived descriptor, polarizability, for each of the 30 compounds, we set polarizability as the dependent variable and performed regression analysis (using *R* software)[28] between polarizability and each of the other atomic descriptors, separately. The relationships between polarizability and the other descriptors are shown in Figure 2: Polarizability significantly correlates positively with the atomic properties: ionization potential (R = 0.41; p = 0.025, 2a), electronegativity (R = 0.69; $p = 2.4 \times 10^{-5}$, 2b), hardness (R = 0.77; $p = 8 \times 10^{-7}$, 2d) and electron affinity (R = 0.76; $p = 1.3 \times 10^{-6}$, 2e). The correlation between polarizability and dipole moment (R = 0.26, p = 0.16, 2f) is however, low. Polarizability correlates negatively with chemical potential (R = –0.69; 2.4×10^{-5}, 2c).

At the atomic scale, polarizability and electronegativity are imperative periodic reactivity descriptors.[29,30] While electronegativity represents the electron attracting power of an atom, polarizability corresponds to the ease of distortion of an electron cloud of an atom resulting in loosely bound electrons.[30,31] Thus, it implies that polarizability is an electron loosening (or releasing) power of an atom.

There are many other factors that influence the intensity of ESI response e.g. analyte and solvent composition, analyte concentration, flow rate, pH, denaturing and non-denaturing solutions, solution- and gas-phase basicity, solution-phase conformation, instrument settings such as ion source type, source voltage, sprayer orifice diameter, and gas pressures. These are reviewed in many publications[3,32]. Here, our computational study delves specifically into the influence of di-substituted supercharging reagents on ESI response and multiple charging.

The relationship between hardness and polarizability[33] and that between electronegativity and polarizability[34] have been demonstrated. A quantitative relationship was formulated between electric dipole polarizability and hardness for atoms and clusters.[35] Our study demonstrated the relationships between the six atomic descriptors and polarizability for di-substituted arene molecules. Equations (3)-(7) show the inter-relatedness among these atomic electronic properties of ionization potential, electronegativity, chemical potential, hardness, electron affinity, and dipole moment. Therefore, expressing polarizability as the dependent variable is a reasonable one. Thus, the more polarizable a molecule is, the higher the likelihood of it inducing an interaction e.g., charge-dipole, charge-charge, dipole-dipole, and in high enough concentration, adduct formation with the protein molecule and, therefore, enhancing the ESI response under the same experimental conditions.

In the ESI environment, during the liquid phase, the net charge of a molecule (e.g., peptide, protein) is primarily determined by its *chemical* properties: the number and kind of ionisable groups, the ionization constant of these groups (as described by the pK_a values) and the pH of the solution. The pK_a of these ionisable groups are, to some extent, affected by the values of the local electrostatic potential arising from other charged groups on the molecule. In the gas phase, however, the values of the apparent gas phase basicity of basic side chains and hence the net charge of ions on a protein produced by ESI are mainly determined by its *physical* properties; that is, the molecular surface area of the protein and the Coulombic repulsion between

Table 1. Gas-phase data[37]: Atomic properties for computing molecular polarizability of the selected di-substituted arene supercharging reagents. The atomic property values were derived from equations (3)-(7)

	Compound name	Abbrev[1]	MP[2] (°C)	Ionization potential (eV)	Electron Affinity (eV)	Chemical potential (μ)	Hardness (η)	Electronegativity (χ)	Dipole (D)	Polarizability (α)
1	2-Chlorophenol*	2-CP	7-8	6.55	0.92	-3.74	-2.81	3.74	3.00	84.64
2	3-Chlorophenol	3-CP	30-34	6.63	0.91	-3.77	-2.86	3.77	3.09	84.82
3	4-Chlorophenol	4-CP	39-43	6.38	0.96	-3.67	-2.71	3.67	2.29	84.60
4	2-Nitrochlorobenzene	2-NCB	31-34	7.74	3.15	-5.45	-2.30	5.45	5.16	97.05
5	3-Nitrochlorobenzene	3-NCB	43-47	7.66	3.07	-5.36	-2.30	5.36	4.20	97.71
6	4-Nitrochlorobenzene	4-NCB	82-86	7.79	2.99	-5.39	-2.40	5.39	3.37	99.77
7	(2-nitrophenyl) methanol	2-NPM	69-74	7.72	2.89	-5.31	-2.42	5.31	4.44	102.21
8	(3-nitrophenyl) methanol	3-NPM	30-33	7.73	2.81	-5.27	-2.46	5.27	5.13	102.38
9	(4-nitrophenyl) methanol	4-NPM	90-95	7.75	2.76	-5.26	-2.49	5.26	6.73	103.63
10	1-(2-nitrophenyl) ethanone	2NP	23-27	7.37	4.01	-5.69	-1.68	5.69	5.14	111.74
11	1-(3-nitrophenyl) ethanone	3NP	76-80	7.49	3.93	-5.71	-1.79	5.71	1.81	112.76
12	1-(4-nitrophenyl) ethanone	4NP	76-80	7.51	3.91	-5.71	-1.80	5.71	3.93	114.28
13	2-Nitrobenzonitrile	2-BZN	108-110	8.47	4.42	-6.45	-2.03	6.45	4.50	101.69
14	3-Nitrobenzonitrile	3-BZN	114-117	8.21	4.34	-6.27	-1.94	6.27	7.19	101.36
15	4-Nitrobenzonitrile	4-BZN	144-147	8.48	4.53	-6.50	-1.97	6.50	0.28	103.79
16	1-(2-Nitrophenyl)ethanol	2-NPE	40-41	7.77	3.89	-5.83	-1.94	5.83	5.60	114.93
17	1-(3-Nitrophenyl)ethanol	3-NPE	57-59	7.42	3.80	-5.61	-1.81	5.61	4.86	114.69
18	1-(4-Nitropheny)ethanol	4-NPE	59-62	7.94	3.89	-5.92	-2.03	5.92	4.61	116.81
19	1-methoxy-2-nitrobenzene	2-NB	9-12	6.99	2.57	-4.78	-2.22	4.78	5.81	103.59
20	1-methoxy-3-nitrobenzene	3-NB	36-38	7.07	3.03	-5.05	-2.02	5.05	4.35	103.57
21	1-methoxy-4-nitrobenzene	4-NB	50-54	7.21	2.79	-5.00	-2.20	5.00	6.37	107.07
22	2-Nitrophenethyl alcohol	2-OH	2	7.76	3.91	-5.84	-1.93	5.84	3.53	115.71
23	3-Nitrophenethyl alcohol	3-OH	45-50	7.26	4.15	-5.71	-1.56	5.71	4.48	114.31
24	4-Nitrophenethyl alcohol	3-OH	59-62	7.89	3.82	-5.86	-2.03	5.86	4.70	117.78
25	2- (trifluoromethyl) phenylmethanol	2-PM	4	7.46	1.57	-4.51	-2.95	4.51	2.83	96.77
26	3- (trifluoromethyl) phenylmethanol	3-PM	9-11	7.72	1.64	-4.68	-3.04	4.68	3.90	97.39
27	4- (trifluoromethyl) phenylmethanol	4-PM	18-20	7.81	1.73	-4.77	-3.04	4.77	1.19	97.98
28	2-Nitrobenzoic acid	2-NBA	146-148	8.02	4.29	-6.15	-1.86	6.15	5.93	103.57
29	3-Nitrobenzoic acid	3-NBA	139-141	8.35	4.35	-6.35	-2.00	6.35	2.78	103.87
30	4-Nitrobenzoic acid	4-NBA	237-240	8.35	4.39	-6.37	-1.98	6.37	2.48	104.99

*For full list of compound references, refer to Abaye *et al*. 2021 (Ref. 3).

[1]Abbreviation for graph plotting purposes. See Figure 2.

[2]Melting points (From Ref. 38 and 39). Boiling points are indicated in Ref. 3.

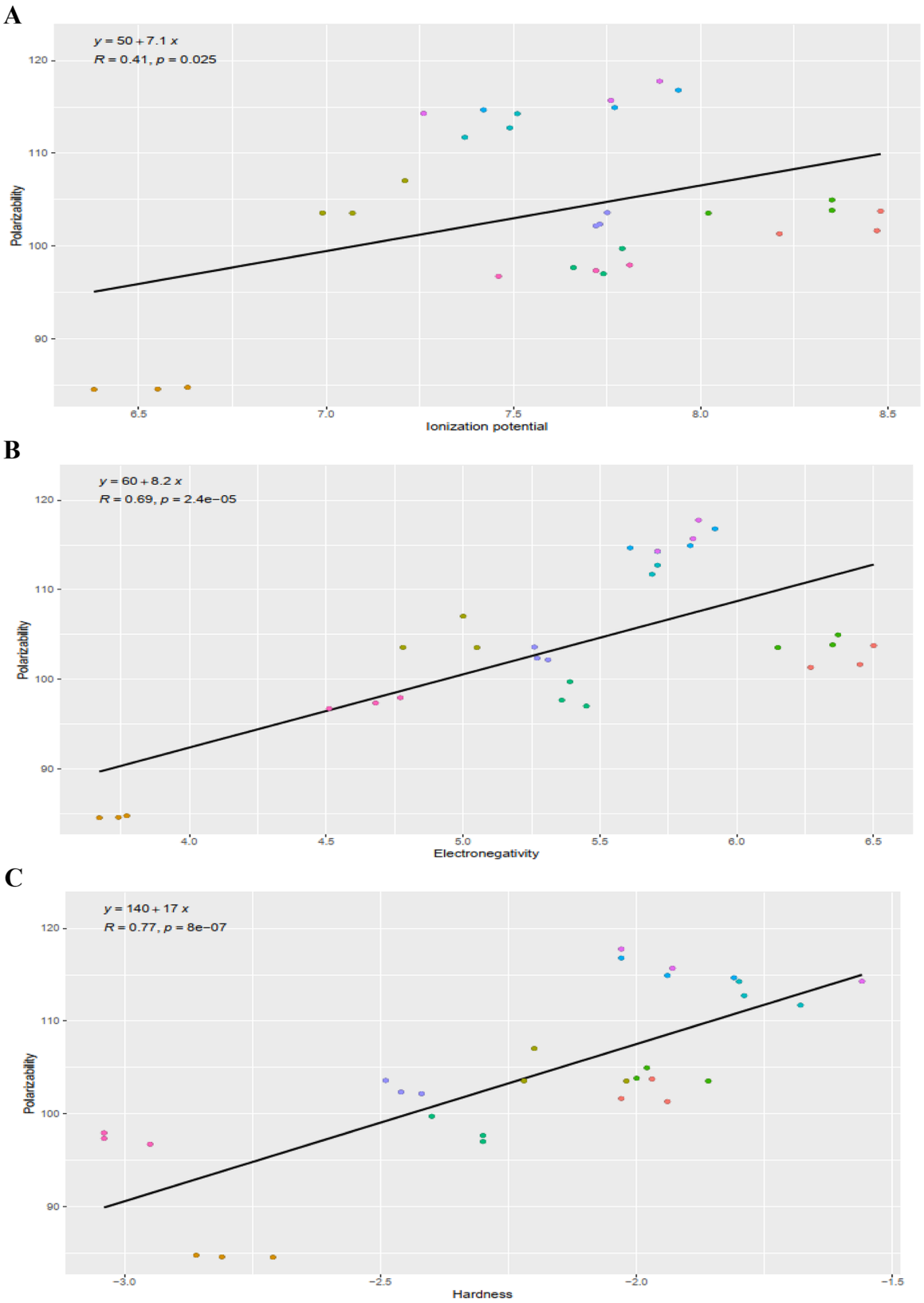

Figure 2. Plots of ionization potential (**A**), electronegativity (**B**), hardness (**C**), electron affinity (**D**), dipole moment (**E**) and chemical potential (**F**) vs. polarizability.

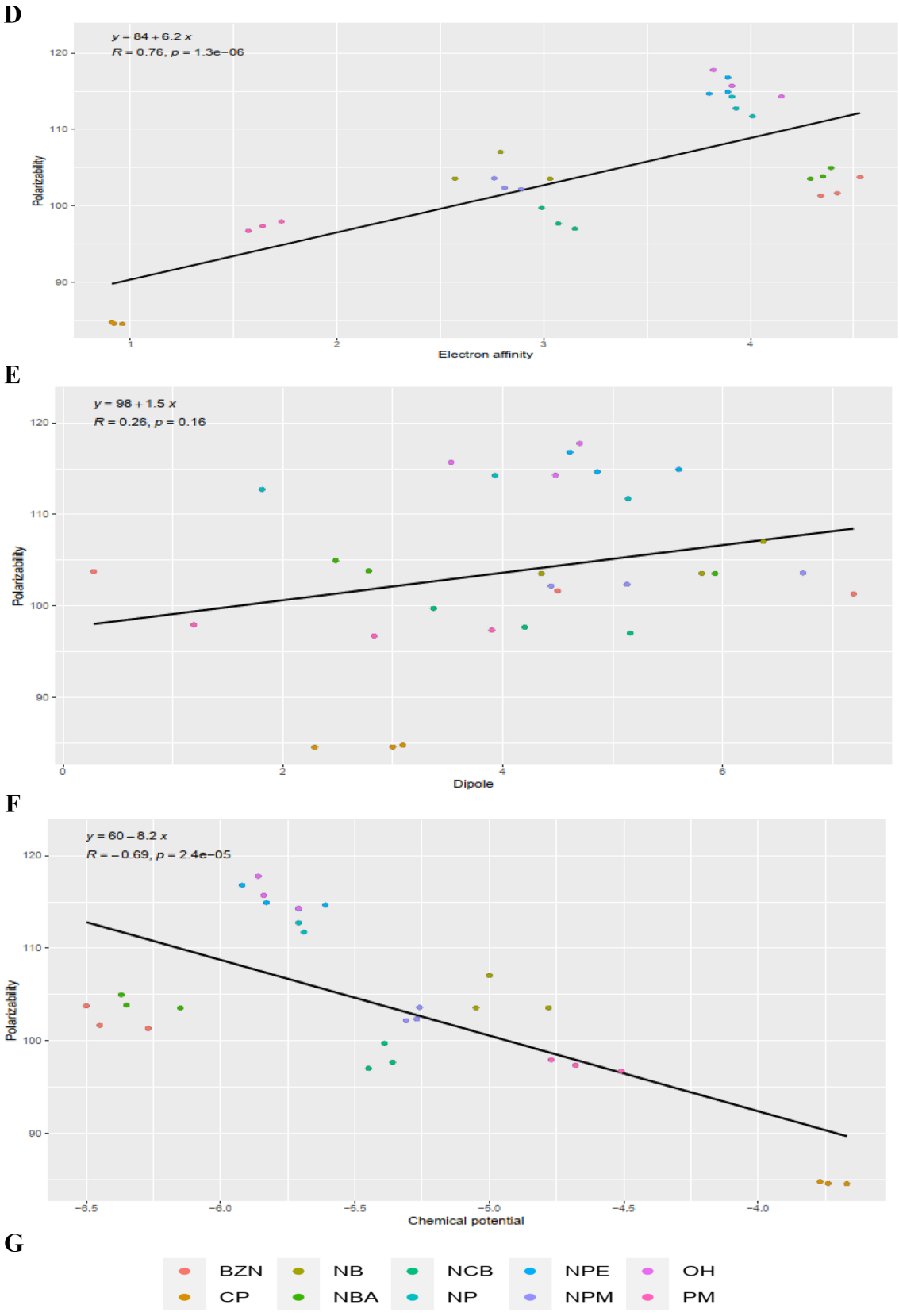

Figure 2. Continued

charged sites on its surface.[36] This fundamental principle applies during the final stages of ionization of protein molecules in the presence of a supercharging reagent in the ESI environment. Thus, in the gas phase, the role of pK_a is greatly diminished compared with those in the liquid phase. Therefore, we did not include pK_a values in these gas-phase calculations.

Conclusions

Our DFT study determined that in di-substituted arene molecules which are or could be used as supercharging reagents during ESI-MS, the *para* isomer of these reagents have the highest polarizability values, except for in one instance and in the simplest set of molecules. Polarizability was also higher for molecules where the substituents were more complex. Polarizability correlated positively with ionization potential, electronegativity, hardness, electron affinity, and dipole moment, although the correlation with dipole moment was low. However, polarizability correlated negatively with chemical potential. Therefore, we submit that during supercharging experiments in ESI, where available, the researcher should opt for the *para* isomer with some degree of complexity in the two substituents to achieve a greater ESI response. Of course, it would be interesting to see an ESI-MS comparison among the three isomers.

Supplementary materials

Further details including data are published and freely available at *Mendeley Data*[37] DOI:10.17632/nvk8hrwgrn.1 https://data.mendeley.com/datasets/nvk8hrwgrn/1

Author Contributions

Daniel A. Abaye (DAA) and Albert Aniagyeia (AA): Conceptualization, Methodology.

DAA, AA, David Adedia (DA), Birthe V. Nielsen (BN), Francis Opoku (FO): Investigation, curation and data interpretation.

DAA, AA, DA: Resources.

DAA: Writing- Original draft.

DAA, AA, BN: Writing-Review & Editing.

All authors approved the final manuscript.

Conflicts of interest

There are no conflicts to declare.

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