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Anisotropic electrostatic models of nitrogen and phosphorus: the variation and the interpretability of the electrostatic parameters in response to structure variation

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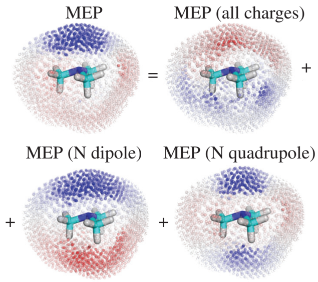
The anisotropic electrostatic parameters of truncated multipole expansion (atomic dipole and quadrupole) obtained for a series of nitrogen and phosphorus containing compounds allow for a reasonable physical interpretation and appear to be predictable in response to chemical substituent variation. These findings will be useful for prediction of anisotropic parameters in next generation force fields without the need to resort to quantum chemical calculations.



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Molecular mechanics force fields have become an inevitable tool for molecular modelling in drug discovery[1,2] and other fields. Despite the current success, the search for better and more detailed description of inter- and intra-molecular interactions is continuing to shape the next generation force fields. The driving force in the area of computer-aided drug discovery is the need to properly describe generally weak but still considerable interactions which are apparently anisotropic, such as halogen bonding (XB)[3–5] for heavy halogens as well as similar interactions for other heteroatoms.[6] The anisotropy of interactions is heavily dependent on their electrostatic part. The quality of electrostatic interaction description could be judged by reproduction of the reference molecular electrostatic potential (MEP).

Nitrogen and phosphorus are abundant in drugs, natural ligands and biotargets, hence their correct treatment is of importance for drug discovery. Nitrogen has been long known in chemistry as a prototypical example of clearly articulated anisotropic feature such as a lone pair. It was shown[7] that amine nitrogen among other elements suffers the most from MEP anisotropy misrepresented by means of atomic point charges, thus urging to seek the relevant solution.

There are several viable general options to introduce anisotropic electrostatics into the force fields and, in particular, the recent attempts to describe amine nitrogen anisotropy *via* extra point charges.[8] However, the most general current state-of-the-art approach is to represent permanent electrostatics by means of the distributed multipole expansion truncated at quadrupole contribution.[9–12]

The question is to which extent the distributed multipole expansion approach is applicable to describe the MEP around amine nitrogen and phosphine phosphorus atoms. Another question is to what extent these parameters are interpretable physically and if they change predictably upon the change in the chemical environment of nitrogen and phosphorus atoms. The latter is important for empirical methods aimed at predicting the anisotropic parameters without resorting to quantum chemical calculations for each molecule.

In this work, we assess the achievable quality of MEP description as well as predictability and interpretability of the anisotropic parameters within the quadrupole truncated series approximation for nitrogen and phosphorus compounds. Previously, this approach applied to the analysis of heavy halogen atoms (pertinent to XB) electrostatic potential led to a clear interpretation of quadrupole correction as a constant internal polarization caused by C–X bond formation.[13,14]

To study anisotropic parameters, a set of small nitrogen and phosphorus containing compounds was created as $X(F)_m(Me)_n(H)_k$, where X is N or P, and $m + n + k = 3$. The substituents were chosen to be small and to widely span the electron donating or withdrawing properties.

The reference MEP was calculated at MP2/aug-cc-pVTZ level. The m-mdzqz anisotropic model was used, in which all atoms were represented with point charges (monopoles, m), whereas nitrogen and phosphorus atoms were additionally represented with atomic dipole (dz) and quadrupole (qz) components aligned along *Z* axis formed by the bisector of all three sigma bond vectors (Figure 1).

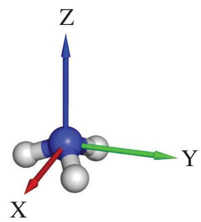

Figure 1 Local multipole axes used for amine N and phosphine P multipole expansion.

Table 1 The residual MEP error and the values of anisotropic multipole parameters for N containing compounds of the training set.

Molecule	MEP error/ kcal mol^{-1} el^{-1}		Anisotropic parameters for models/a.u.			
	m-m	m-mdzqz	m	m-mdzqz		
				m	dz	qz
NF_3	1.21	0.65	0.09	0.43	–0.36	–0.60
NF_2CH_3	1.55	0.84	–0.09	0.38	–0.42	–1.00
NF_2H	1.69	1.00	–0.31	0.18	–0.38	–0.93
NFH_2	1.89	1.12	–0.63	–0.17	–0.31	–1.14
$NFCH_3H$	2.02	1.29	–0.45	0.18	–0.50	–1.34
$NF(CH_3)_2$	1.57	0.83	–0.09	0.39	–0.47	–1.53
$N(CH_3)_3$	1.47	0.64	–0.07	0.41	–0.45	–2.02
$NH(CH_3)_2$	2.25	1.48	–0.54	0.19	–0.62	–1.85
NH_2CH_3	2.37	1.60	–0.86	–0.19	–0.45	–1.58
NH_3	1.98	0.36	–0.92	–0.95	0.05	–0.86
Mean	1.80	0.98	–0.39	0.09	–0.39	–1.29
Std. dev.	0.36	0.39	0.35	0.43	0.18	0.46

The multipole MEP was modelled according to formula (1)

$$V_i = \sum_j^{Natoms} \frac{q_i}{|\mathbf{R}_{ij}|} + \frac{\mathbf{R}_{ia}\mathbf{d}}{|\mathbf{R}_{ia}|^3} + \frac{\mathbf{R}_{ia}^{\mathrm{T}}\mathrm{Q}\mathbf{R}_{ia}}{|\mathbf{R}_{ia}|^5}, \qquad (1)$$

where V_i is the potential in the i-th grid point; $\mathbf{R}_{ij}$ is vector from i-th grid point to j-th atom; q_j is charge on j-th atom; $\mathbf{R}_{ia}$ is vector from i-th grid point to N or P atom, expanded with the dipole vector **d** and quadrupole matrix Q with the components described in Online Supplementary Materials.

To estimate the enhancement in quality brought by the introduction of multipoles on N and P atoms, a charge only model (m-m in Tables 1 and 2) was parameterized separately with the MEP described by the first term of equation (1).

The simplified Hansch type equation (2) was used to correlate the anisotropic parameters.

$$p_i = a\ \mathrm{count}_i(\mathrm{F}) + b\ \mathrm{count}_i(\mathrm{C}) + c, \qquad (2)$$

where p_i is the dependent (reference) anisotropic parameter for i-th molecule; a, b, c are the coefficients sought by the regression; count$_i$(F) is the number of fluorine atoms, whereas count$_i$(C) is the number of carbon atoms (or CH_3 groups) in i-th molecule.

In all cases the residual MEP error reduces significantly (1.8 to 3.1 times) for N and P compounds when the anisotropic multipole model m-mdzqz is applied compared to the charge only model m-m (Tables 1 and 2).

Table 2 The residual MEP error and the values of anisotropic multipole parameters for P containing compounds of the training set.

Molecule	MEP error/ kcal mol^{-1} el^{-1}		Anisotropic parameters for models/a.u.			
	m-m	m-mdzqz	m	m-mdzqz		
				m	dz	qz
PF_3	2.26	0.57	0.41	1.02	–0.96	–1.41
PF_2CH_3	2.66	0.67	0.11	0.90	–1.18	–1.86
PF_2H	3.12	1.55	–0.18	0.56	–0.82	–2.11
PFH_2	3.01	1.27	–0.42	0.41	–0.76	–2.95
$PFHCH_3$	3.14	1.29	–0.35	0.50	–0.90	–2.75
$PF(CH_3)_2$	2.93	0.66	–0.08	0.79	–1.28	–2.40
$P(CH_3)_3$	3.06	0.56	–0.15	0.65	–1.28	–2.94
$PH(CH_3)_2$	3.17	1.00	–0.44	0.42	–0.91	–3.31
PH_2CH_3	2.99	1.19	–0.57	0.21	–0.71	–3.26
NH_3	2.78	0.63	–0.54	–0.10	–0.32	–2.72
Mean	2.91	0.94	–0.22	0.53	–0.91	–2.57
Std. dev.	0.28	0.36	0.31	0.33	0.29	0.62

Table 3 Parameters of the Hansch-type correlations (2) of the anisotropic multipole model components with substituent variation for amine N compounds. Estimated parameter significance levels are in parentheses: h – high, m – moderate, s – satisfactory, l – low.

p	R^2	stderr	R^2_{adj}	F	a	b	c
m	0.91	0.14	0.89	36.12	0.39 ± 0.05 (h)	0.39 ± 0.05 (h)	–0.7 ± 0.1 (h)
dz	0.48	0.14	0.34	3.276	–0.07 ± 0.05 (l)	–0.13 ± 0.05 (s)	–0.2 ± 0.1 (l)
qz	0.91	0.16	0.88	35.31	0.15 ± 0.06 (s)	–0.31 ± 0.06 (m)	–1.1 ± 0.1 (h)

Table 4 Parameters of the Hansch-type correlations (2) of the anisotropic multipole model components with substituent variation for phosphine P compounds. Estimated parameter significance levels are in parentheses: h – high, m – moderate, s – satisfactory, l – low.

p	R^2	stderr	R^2_{adj}	F	a	b	c
m	0.97	0.06	0.97	125.6	0.35 ± 0.02 (h)	0.24 ± 0.02 (h)	–0.06 ± 0.04 (l)
dz	0.94	0.08	0.92	50.65	–0.22 ± 0.03 (h)	–0.30 ± 0.03 (h)	–0.39 ± 0.06 (h)
qz	0.86	0.26	0.82	21.95	0.56 ± 0.09 (h)	0.04 ± 0.09 (l)	–3.2 ± 0.2 (h)

The main result is that anisotropic components predictably (R^2 values in Tables 3 and 4) change upon substituent variation on N and P atoms. Thus, the anisotropic components appear to have a reasonable physical interpretation.

First, atomic dipole moment can be interpreted as an internal polarization caused by the presence of a lone pair orbital, which is supported by negative value (dz in Table 1), and hence the MEP, in the direction of the lone pair. For practical considerations, the atomic dipole (dz) for N can be fixed at the value near –0.4 a.u. (1.0 D). The dipole moment component, dz, for P is more affected by the substitution of H with F or Me, since P is 'softer' (less 'hard') in terms of Pearson's definition.[15]

Second, the quadrupole component variation could be interpreted as the variation in excess of electronic density, caused by the substituents with +I and –I effects. The negative lobe of the quadrupoles in all fits is directed toward the lone pair axis. Substitution with F atoms always causes quadrupole component to be less pronounced, with a larger influence for P compounds due to higher electronegativity difference between P and F. Substitution with Me leads to the enhancement of quadrupole component for N compounds and has almost no effect for P compounds in accord with the electronegativity differences of Me group and N/P atoms, respectively. For practical simplified calculations, a fixed mean value of quadrupole qz for different structures of *ca.* –2.6 a.u. (3.5 B) can be used, since its variation is less than the value of the constant term *c*.

A significant quality enhancement is found upon switching from isotropic charge only model to anisotropic multipole based model, with MEP error reduction of factor 1.8 and 3.1 for amine nitrogen and phosphine phosphorus compounds, respectively. The anisotropic parameters allow for a reasonable physical interpretation, whereas the variation of those parameters with the variation of the chemical nature of substituents was shown to be predictable in principle. The latter opens the way for empirical prediction of anisotropic parameters for arbitrary nitrogen and phosphorus containing molecules without resorting to quantum chemical calculation for each molecule, *e.g.*, using electronegativity based approach for charge calculation.[16]

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.11.017.

References

1 X. Liu, D. Shi, S. Zhou, H. Liu, H. Liu and X. Yao, *Expert Opin. Drug Discov.*, 2018, **13**, 23.
2 J. D. Durrant and J. A. McCammon, *BMC Biol.*, 2011, **9**, 71.
3 N. K. Shinada, A. G. de Brevern and P. Schmidtke, *J. Med. Chem.*, 2019, **62**, 9341.
4 P. Politzer and J. S. Murray, *ChemPhysChem*, 2013, **14**, 278.
5 P. Politzer, J. S. Murray and T. Clark, *Phys. Chem. Chem. Phys.*, 2010, **12**, 7748.
6 P. Politzer, J. S. Murray and T. Clark, *Phys. Chem. Chem. Phys.*, 2013, **15**, 11178.
7 C. Kramer, A. Spinn and K. R. Liedl, *J. Chem. Theory Comput.*, 2014, **10**, 4488.
8 A. Spinn, P. H. Handle, J. Kraml, T. S. Hofer and K. R. Liedl, *J. Chem. Theory Comput.*, 2020, **16**, 4443.
9 C. Liu, J.-P. Piquemal and P. Ren, *J. Chem. Theory Comput.*, 2019, **15**, 41.
10 S. Cardamone, T. J. Hughes and P. L. A. Popelier, *Phys. Chem. Chem. Phys.*, 2014, **16**, 10367.
11 S. Jakobsen, T. Bereau and M. Meuwly, *J. Phys. Chem. B*, 2015, **119**, 3034.
12 D. A. Shulga, O. I. Titov, S. A. Pisarev and V. A. Palyulin, *SAR QSAR Environ. Res.*, 2018, **29**, 21.
13 O. I. Titov, D. A. Shulga, V. A. Palyulin and N. S. Zefirov, *Mol. Inf.*, 2015, **34**, 404.
14 O. I. Titov, D. A. Shulga and V. A. Palyulin, *J. Chem. Theory Comput.*, 2019, **15**, 1159.
15 R. G. Pearson, *Acc. Chem. Res.*, 1993, **26**, 250.
16 D. A. Shulga, A. A. Oliferenko, S. A. Pisarev, V. A. Palyulin and N. S. Zefirov, *SAR QSAR Environ. Res.*, 2008, **19**, 153.

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