

Procedure of Computing Partial Charges of Carcinogen-Modified B-Deoxynucleotides

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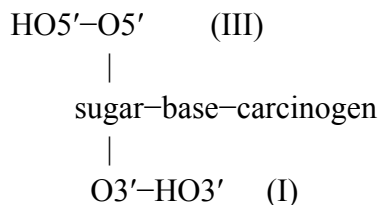
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1. Build two molecules [InsightII]

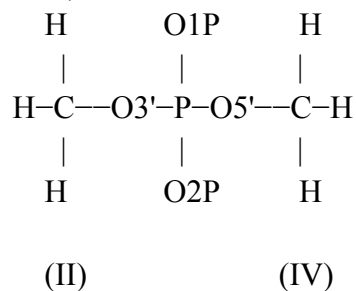
To make our partial charges compatible with AMBER's force field, we calculate partial charges of the following two molecules, similar as AMBER does. Finally we will combine the partial charges of these two molecules in Step 5. We use InsightII (Accelrys) to build these two molecules.

A. Nucleoside with carcinogen



- Cap 5' and 3'-end (no phosphate group).
- Set dihedral angles:
 - β (HO5'-O5'-C5'-C4') = 180.0°
 - ε (C4'-C3'-O3'-HO3') = 180.0°
 - γ (O5'-C5'-C4'-C3') = 58.5 (DA, DA5, DA3)
= 58.9 (DC, DC5, DC3)
= 58.5 (DG, DG5, DG3)
= 58.4 (DT, DT5, DT3)
- No bumps.

B. Dimethylphosphate (DMP)



- Set dihedral angles
 $\text{C-O3}'-\text{P-O5}' = -73.1^\circ$
 $\text{O3}'-\text{P-O5}'-\text{C} = -73.1^\circ$
(Reference 1 used positive dihedral angles. But in regular A- and B-DNA, these dihedral angles are negative, i.e. (g⁻, g⁻) conformation.)
- No bumps.

2. Optimize geometry on each molecule [Gaussian]

The geometry optimization of both molecules will be performed in next step as the electrostatic potentials (ESP) are calculated simultaneously in Gaussian. The time of Gaussian calculation with optimization option will be quite long (~1 week) on the nucleoside with carcinogen. (The optimized structures can be used for building topology files for AMBER, if one needs to do molecular dynamics.) If you want to calculate the partial charges on a specific structural conformation, you may skip this step.

3. Calculate electrostatic potential (ESP) on each molecule [Gaussian]

How to build Gaussian input files can be found in the Gaussian Manual (Reference 2). Following are a few parameters which have to be set in Gaussian input files.

- Route section (HF/6-31G*, ESP output, optimization; remove “opt” if you want to calculate the partial charges on a specific structural conformation):
`# HF/6-31G* pop=(minimal,mk) opt maxdisk=134217728 iop(6/33=2)`
- Charge = 0 (nucleoside with carcinogen, if carcinogen has zero charge), or
= -1 (dimethylphosphate).
- Spin multiplicity = $N_{up}+1$ (N_{up} is the number of unpaired electrons; ground state).

4. Check interactions in optimized structures [InsightII]

Gaussian does not know where bonds, angles, and dihedral angles are if we do not tell in the input files. So the optimized structures may have unreasonable interactions. We use InsightII to check bumps in the optimized structures. If all the interactions are reasonable, we can go to next step. Otherwise, we have to restart from Step 1 (or the current optimized structures) by manually adjusting the structures to avoid further unreasonable interactions.

5. Calculate partial charges of both molecules together [RESP]

Now we need to combine ESP of these two molecules together to calculate the partial charges of the carcinogen modified nucleotide within two stages of AMBER's RESP. See AMBER Manual (Reference 3) for how to build the input files for RESP. The partial charges of the phosphate group (P, O1P, and O2P) will be taken from the dimethylphosphate (DMP).

A. First stage

- Charge constraints
 - I + II = 0 (DX5, X = A, C, G, or T. Partial charge of O3' will be taken from DMP),
or
 - III + IV = 0 (DX3. Partial charge of O5' will be taken from DMP), or
 - I + II = III + IV = 0 (DX. Partial charges of O3' and O5' will be taken from DMP).
- O1P, O2P in phosphate group are equivalenced.
- H in NH₂ groups are equivalenced.
- Hyperbolic restraints with a force constant a = 0.0005 are applied to all heavy atoms, and hydrogens are not restrained.

B. Second stage

- CH₂ and CH₃ in nucleoside are refit; other atoms' charges are kept.
- Hyperbolic restraints with a force constant a = 0.001 are applied to only the carbons of CH₂ and CH₃ in nucleoside, and hydrogens are not restrained.
- H in CH₂ or CH₃ in nucleoside are equivalenced.

Notes:

- The final total charge of the carcinogen modified nucleotide will be exactly -1.0000 for DX types (X = A, C, G, or T), if the carcinogen has zero charge.
- This procedure can be easily applied to A-deoxynucleotides and A-ribonucleotides with Reference 1.
- Perl programs and a sample are available at <http://monod.biomath.nyu.edu/~qzhang/Research.htm>

Acknowledgments:

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References:

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Citation:

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