

Implementation of a method for calculating relative free energies for a general force field

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Abstract

In the following manuscript we describe the implementation of a method for calculating relative free energies for a general force field (A simple, robust and efficient method for calculating relative free energies).

Common Denominator Theorem

The following is a description of how to transform a group of similar molecules (e.g phenol derivatives) according to the method described in the article.

Similar groups (e.g benzene and phenol derivatives) can either be grouped together or linked later on (preferably the second option) and so on.

The goal here is to satisfy the following:

1. Performing an exact calculation.
2. Performing a calculation that can be automated.
3. Performing a general calculation, applicable to all the existing force fields.
4. Performing the smallest transformations possible.
5. Performing a transformation that will necessarily result in a monotonic change in the integrated function.
6. Performing a transformation that will only necessitate one transformation of each molecule at each environment.

In order to satisfy all of the above, we will focus on two groups of potential terms:

1. Different terms that belong to the common sub system.
2. Terms that couple the common sub system to the different sub system.

The guiding rule for the transformation will be to transform the existing terms in the common sub system up to the common denominator (which we will define later on). Transforming terms of the common sub system will be by either of the two strategies:

- In the end state the terms will be multiplied by positive numbers in the range $[0, 1]$ (do not have to be equal among terms) or
- In the end state the terms will be multiplied by numbers in the range $[-\infty, 1]$ (do not have to be equal among terms).

Both strategies will ensure that the change in the integrated function will be monotonic. The first one has the advantage that it will be according to the formalism of the method and the second one has the advantage of enabling in some cases overall a smaller transformation.

The two strategies can be summarized as follows:

For two values a and b of partial charge or VDW parameters we will have the new values new_a and new_b according to the following rules.

if a and b have the same sign

new_a and new_b will get the value among them having the smaller absolute value.

if a and b have different sign

first strategy:

new_a and new_b will be set to zero.

second strategy:

new_a and new_b will be set to the average of a and b .

The common denominator will satisfy the following:

1. The common sub system will be identical between all the systems.
2. The two sub systems will be decoupled.

The rules for performing the transformation are the following:

1. Different terms that belong to the common sub system will be transformed according to one of the two strategies. For the first strategy if the term has a different sign among the molecules, as can be only in the case of partial charge, it will be completely relaxed.
2. Terms that belong to the different sub systems and do not couple between the systems will not be transformed.
3. Terms that couple the common sub system to the different sub system will be completely relaxed. These terms usually include the non bonded terms and improper dihedral/s. However the identification of these terms is a subtle issue.

Demonstration

We will now demonstrate the method for comparing the solvation free energy of Crestol and Chloro-para-Phenol.

We will present on the illustration only the terms that will be transformed (the rest will be terms that are identical in the common sub system and terms of the different sub system that do not couple between the systems). Similar transformations apply for a group of 3,4 etc. para-phenols (the terms of all the molecules have to be taken into account).

We will use an auto-generated force field presented in the article: An Automated force field Topology Builder (ATB) and repository/ JCTC 2011, 7(12). This type of force field is the most varying among similar molecules and it was chosen in order to show the generality of the method.

We will not present the VDW terms in order to have a clearer figure. These terms are simpler to transform as compared with the partial charge as they do not change sign.

Figure 1: Illustration of the transformations to the common denominator - first strategy

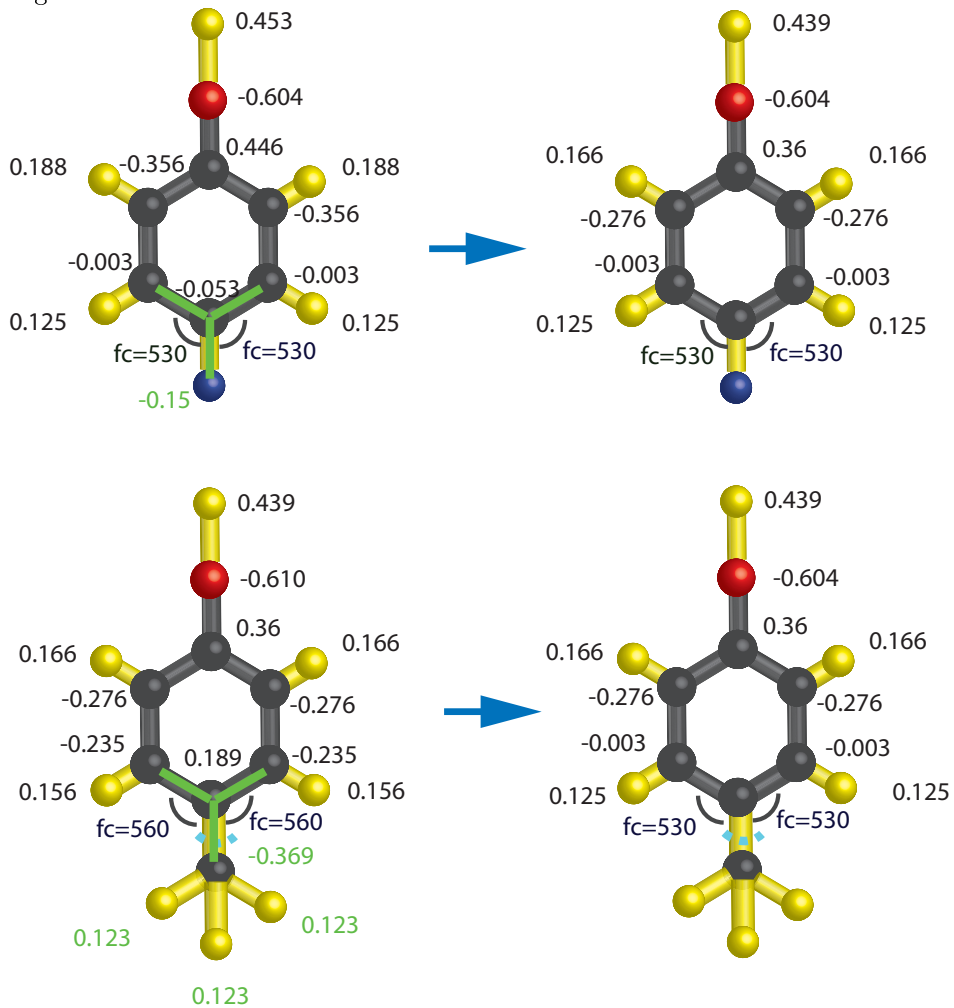
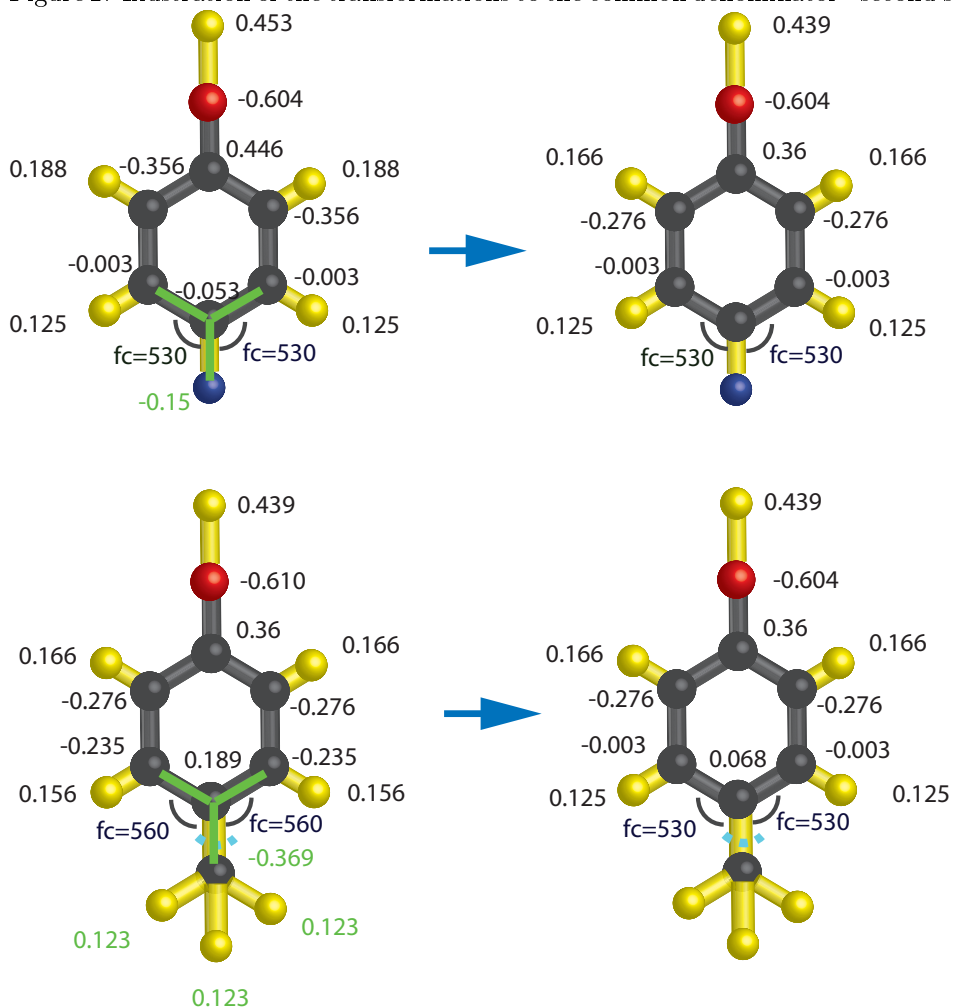


Figure 2: Illustration of the transformations to the common denominator - second strategy



In Figure 1 and 2 illustrations of the transformations to the common denominators are presented. In case there does not appear a term its value is zero. The terms in black are the terms that belong to the common sub system. The terms in green are the coupling terms and the term in light blue is the dihedral term (dashed line). The partition function of this dihedral term is independent of the partition function of the transformed common sub system (it can also be effectively associated with the different sub system). As a result it will cancel out between the same molecule in the two environments and can remain constant. It is noted that the angle terms marked on the figure have the same values of average angle and different values of the spring constant (corresponds to f_c) which after the transformation are the same. The three connected green lines represent the

improper dihedral term that couples between the two sub systems and will be relaxed in the transformation. It is emphasized that the treatment will be much simpler in standard force fields in which the common sub system is usually identical or nearly identical and this example is given in order to show the general case.