

## ADDITIVITY SCHEMES IN CONFORMATIONAL ANALYSIS. CONCEPT AND DEMONSTRATION

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Received 26 September 2004

Accepted 23 November 2004

Additivity schemes are of fundamental importance in molecular modeling. It is the goal of an additivity scheme to predict the value of parameter for a complex system based on the knowledge of the respective parameters for prototypical systems. The commonly employed method is based on the identification of energy factors, the quantification of these energy factors, and the evaluation of trial functions that depend on these factors. We describe a non-iterative method to derive energy factor expressions. While energy factors occur in the derivation of the energy factor expressions, the values of the energy factors are not determined and they are expressed instead as series of the known parameters of the minimal set of prototypes. The non-iterative energy factor analysis is illustrated by application to conformational preference energies for a series of spiro(THF)cyclohexanes for which the results of a traditional analysis are available. We demonstrate that the contributions to the conformational preference energy are additive, clarify the precise meaning of the terms “*gauche* interaction” and “1,3-interaction”, and state a more general hypothesis that provides opportunities for testing by future experimental and computational studies.

*Keywords:* Conformational analysis; additivity schemes; cyclohexane; *gauche* interaction; 1,3-interaction.

### 1. Introduction

Additivity schemes are of fundamental importance in molecular modeling. It is the goal of an additivity scheme to predict the value of a parameter for a complex system based on the knowledge of the respective parameters for prototypical systems. Here, we will be concerned with the parameter “preference energy” and Fig. 1 illustrates two conceptual approaches. A set of preference energies  $PE_n$  is given and the goal is the derivation of an energy factor expression that connects the preference energy of the complex system with “factors” derived from a minimal set of prototypical systems. The data set in Fig. 1 contains the  $PE_n$  data for all  $n$  values and this is the desired situation to evaluate the validity of derived energy factor expressions. Once validated in this sense, the energy factor expressions can then be considered

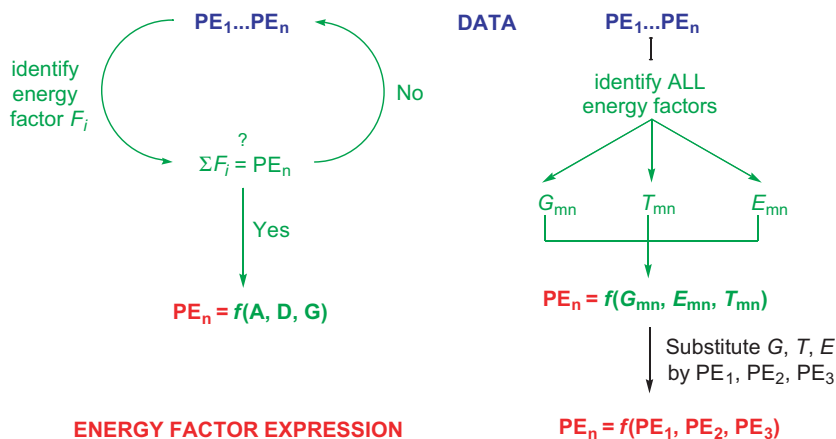


Fig. 1. Schematic depiction of approaches.

to be generally valid and used to predict  $PE_m$  values for still more complex systems ( $m > n$ ).

The commonly employed method for energy factor analysis of conformational preference energies is depicted on the left in Fig. 1. An energy factor is identified, e.g. axial versus equatorial preference energy, and it is then examined whether all  $PE_n$  can be expressed as functions of this first energy factor,  $F_1$ . This is not case, of course, and a second factor  $F_2$  is identified in the second loop, e.g. a 1,2-interaction term such as the *gauche* effect. Again, the examination is made as to whether all  $PE_n$  can be expressed as functions of these two energy factors. This process continues until enough factors  $F_i$  have been identified to obtain close agreement between the actual  $PE_n$  data and the approximated  $PE_n$  data determined with the energy factor expression. The non-iterative linear method to derive energy factor expressions is depicted on the right in Fig. 1. This methods starts with the identification of all two-body interactions. Three types of interactions are considered here, they are denoted  $G$  (1,2-*gauche* term),  $T$  (1,2-*trans* term), and  $E$  (1,3-term), and other terms could be considered as well (e.g. transannular interactions). The energy factor expression is then written as the sum of the two-body interactions. And here is one point in which the approaches differ in a significant way: while the loop method assigns actual values to the factors, the non-iterative method expresses the factors as a series of the known parameters of the minimal set of prototypes.

In the present paper, we illustrate the non-iterative energy factor analysis by its application to derive energy factor expressions for conformational preference energies for a series of spiro(THF)cyclohexanes (Fig. 2) for which the results of a triaditional analysis already are available. Rablen, Paquette, and Borden expertly discussed the conformational preferences of spiro(THF)-cyclohexanes, **1–12**.<sup>1</sup> It was one of the aims of the RPB study to explain the observation that all-*trans*-1,2,3,4,5,6-hexaspiro(THF)cyclohexane, **12**, prefers the all-*O*-equatorial

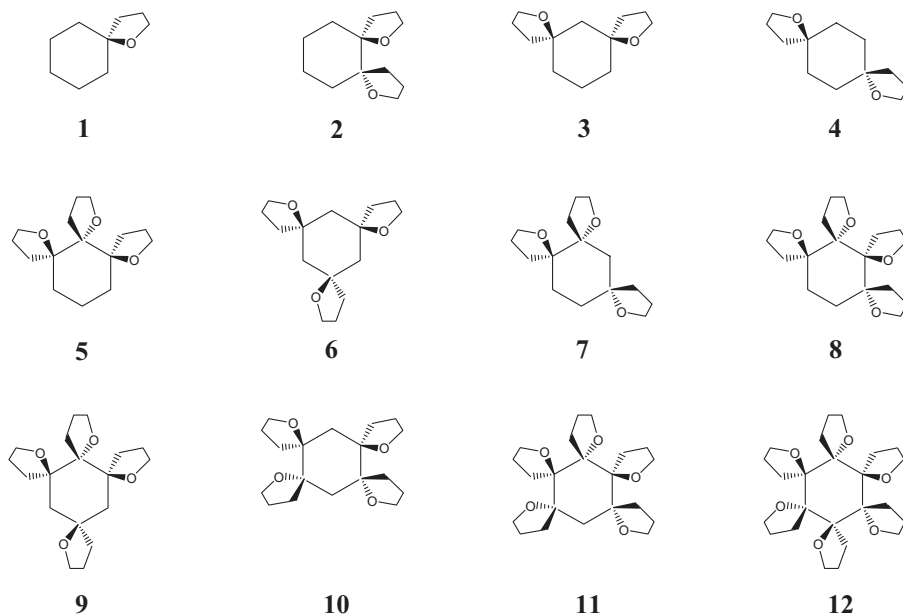


Fig. 2. Nomenclature.

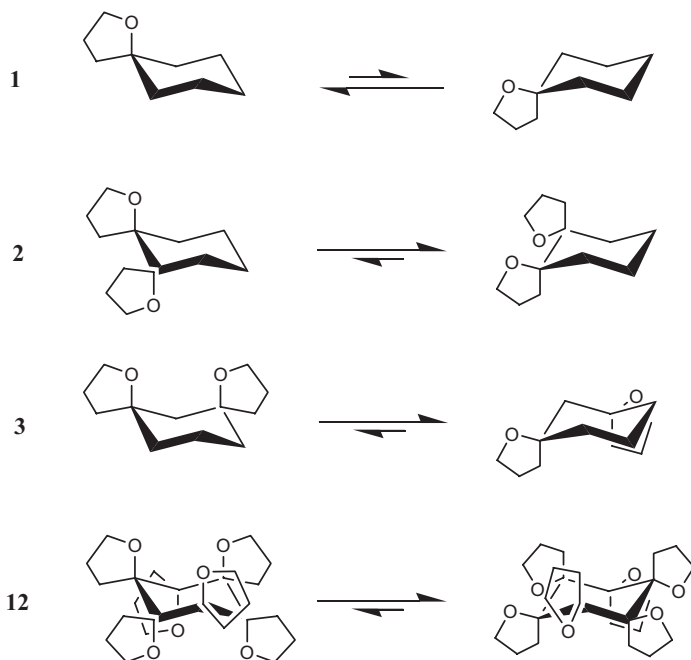
conformation,<sup>2,3</sup> while monospiro(THF)-cyclohexane **1** prefers the *O*-axial conformation.<sup>4</sup> RPB discussed the conformational preference energies considering three factors, the conformational preference energy of **1**, the *gauche* effect, and the 1,3-diaxial effect. For ease of comparison, we adopt the RPB nomenclature (Fig. 2) and we base our analysis on their data (see Table 2).

## 2. Derivation of Energy Factor Expressions

In considering an additivity scheme for the calculation of the interactions among the substituents of **12**, one needs to consider all of the pair-wise interactions that occur in **12** and then find the simplest compounds that contain everyone of those interactions individually (if possible). Since **12** contains interactions that also exist in **1**, **2**, and **3**, respectively, it should be possible to explain the behavior of **12** based on the properties of **1**, **2**, and **3** (Fig. 3).

There are four distinct two-body interactions in **12**. For the *O*-axial conformation, they are 1,2-alkoxy-alkyl *gauche*, 1,2-alkyl-alkyl *gauche*, 1,2-alkoxy-alkoxy *trans*, and 1,3-alkoxy-alkoxy interactions and we refer to these interactions as  $G_{o,a}$ ,  $G_{a,a}$ ,  $T_{o,o}$ , and  $E_{o,o}$ , respectively, where the subscripts “*o*” and “*a*” refer to alkoxy and alkyl groups, respectively. For the *O*-equatorial conformation, they are 1,2-alkoxy-alkyl *gauche*, 1,2-alkoxy-alkoxy *gauche*, and 1,2-alkyl-alkyl *trans*, and 1,3-alkyl-alkyl interactions ( $G_{o,a}$ ,  $G_{o,o}$ ,  $T_{a,a}$ , and  $E_{a,a}$ , respectively).<sup>5,a</sup> The

<sup>a</sup>The *trans* terms  $T$  account for any  $\sigma \rightarrow \sigma^*$  interactions.

Fig. 3. Conformations (cf. Rablen *et al.*<sup>1</sup>).

preference energy between the two conformations can thus be calculated by the following equation.

$$PE_{12} = 6 \times (G_{o,o} - G_{a,a}) + 12 \times (G_{o,a} - G_{o,a}) + 6 \times (T_{a,a} - T_{o,o}) + 6 \times (E_{a,a} - E_{o,o}). \quad (1)$$

Equation (1) is an expansion of the preference energy that contains all 1,2-interactions (first three terms) and all diaxial 1,3-interactions (fourth term). Since the number and kind of *gauche* alkoxy-alkyl 1,2-interactions is the same in both conformations, the second term vanishes<sup>b</sup> and we obtain Eq. (2).

$$PE_{12} = 6 \times (G_{o,o} - G_{a,a}) + 6 \times (E_{a,a} - E_{o,o}) + 6 \times (T_{a,a} - T_{o,o}). \quad (2)$$

The key feature of our analysis consists in the recognition that the terms in this equation for  $PE_{12}$  can be expressed as a sum over the preference energies of compounds **2** and **3**.

$$PE_2 = 4 \times (E_{a,H} - E_{o,H}) + (G_{o,o} - G_{a,a}) + 2 \times (G_{o,a} - G_{o,a}) + 2 \times (G_{o,H} - G_{a,H}) + 2 \times (T_{a,H} - T_{o,H}) + (T_{a,a} - T_{o,o}), \quad (3)$$

<sup>b</sup>This assumes that structural parameters are similar for the various isomers. If this assumption does not hold, then the greater assumption of pair-wise additivity of course also no longer holds. Hence, any additivity analysis relies on this assumption.

$$PE_2 = 4 \times (E_{a,H} - E_{o,H}) + (G_{o,o} - G_{a,a}) + (T_{a,a} - T_{o,o}) \\ + 2 \times (G_{o,H} - G_{a,H}) + 2 \times (T_{a,H} - T_{o,H}), \quad (4)$$

$$PE_3 = (E_{a,a} - E_{o,o}) + 2 \times (E_{a,H} - E_{o,H}) + 4 \times (G_{o,H} - G_{a,H}) \\ + 4 \times (T_{a,H} - T_{o,H}). \quad (5)$$

The sum of the equations for  $PE_2$  and  $PE_3$  can be expressed as a function of  $PE_{12}$  as follows,

$$PE_2 + PE_3 = PE_{12}/6 + 6 \times (E_{a,H} - E_{o,H}) + 6 \times (G_{o,H} - G_{a,H}) \\ + 6 \times (T_{a,H} - T_{o,H}) \quad (6)$$

$$PE_2 + PE_3 = PE_{12}/6 + 3 \times PE_1,$$

where

$$PE_1 = 2 \times (E_{a,H} - E_{o,H}) + 2 \times (G_{o,H} - G_{a,H}) + 2 \times (T_{a,H} - T_{o,H}). \quad (7)$$

Thus, we arrive at

$$PE_{12} = 6 \times (PE_2 + PE_3 - 3 \times PE_1). \quad (8)$$

Using the same approach, we also calculated the conformational preference energies of **4–11** and the derived energy factor expressions are presented in Table 1. The results of the application of these energy factor expressions are listed in Table 2 and four columns of data are reported for every theoretical level. The data in the column “calc.” give the conformational preference energies that are directly computed based on the *ab initio* calculations. The numbers in columns “mod.” are the conformational preference energies derived from our additivity model based on the energy factor expressions of Table 1. The values in the column “diff.” denote the difference between the model data (“mod.”) and the directly computed *ab initio* values (“calc.”). Finally, the  $\Delta$  values give the deviation between our “diff.” value and the respective value in Rablen *et al.*<sup>1</sup>

Table 1. Energy factor expressions.

Compd.	Subst. Pattern	Energy Factor Expression, $PE_n$
<b>1</b>	1	$PE_1$
<b>2</b>	1,2	$PE_2$
<b>3</b>	1,3	$PE_3$
<b>4</b>	1,4	$2 PE_1$
<b>5</b>	1,2,3	$2 PE_2 + PE_3 - 3PE_1$
<b>6</b>	1,3,5	$3 PE_3 - 3PE_1$
<b>7</b>	1,2,4	$PE_2 + PE_3 - PE_1$
<b>8</b>	1,2,3,4	$3 PE_2 + 2PE_3 - 6PE_1$
<b>9</b>	1,2,3,5	$2 PE_2 + 3PE_3 - 6PE_1$
<b>10</b>	1,2,4,5	$2 PE_2 + 2PE_3 - 4PE_1$
<b>11</b>	1,2,3,4,5	$4 PE_2 + 4PE_3 - 11PE_1$
<b>12</b>	1,2,3,4,5,6	$6 PE_2 + 6PE_3 - 18PE_1$



### 3. Discussion

#### 3.1. Numerical validation of the additivity approach

For most of the compounds **4–12**, the non-iterative additivity model reproduces the *ab initio* results very well. The deviations are less than 3 kcal/mol in most cases and only for **6** are they greater than 4 kcal/mol. These deviations reflect structural differences and the neglect of three- and other multi-body effects in the additivity model.<sup>c</sup> The  $\Delta$  values allow for a direct comparison between our non-iterative model and the model applied by RPB. Most of the  $\Delta$  values are rather small in magnitude; generally less than 0.3 kcal/mol and less than 0.1 kcal/mol in most cases.<sup>d</sup>

With the data for  $PE_1$ ,  $PE_2$ , and  $PE_3$  computed at the B3LYP/6-31G\* level, the energy factor expression leads to a value of  $PE_{12} = -20.5$  kcal/mol (last line in Table 2), and the same evaluation with the MP2/6-311+G\*\* data yields  $PE_{12} = -22.3$  kcal/mol. Both of these values reproduce the directly computed preference energy of  $PE_{12} = -22$  kcal/mol very well.

In particular, we wish to point out that here, there is no “unexpected behavior” of **12**. RPB should not have placed such emphasis on the contraposition of the facts that **12** prefers the all-*O*-equatorial conformation by 22 kcal/mol while **1** prefers the *O*-axial conformation by 0.7 kcal/mol. There is no dilemma. It is not reasonable to assume that the inherent steric preference of **12** can be approximated as  $6 \times 0.7 = 4.2$  kcal/mol because the origins of the steric repulsions in **1** and **12** are completely different: the interactions in **12** are due to 1,3-alkoxy-alkoxy repulsion and/or 1,3-alkyl-alkyl repulsion, respectively, while the interactions in **1** are due to 1,3-alkoxy-hydrogen repulsion and/or 1,3-alkyl-hydrogen repulsion, respectively. Only with the consideration of all the important interactions, including the 1,2- and 1,3-interactions is it possible to provide an explanation.

#### 3.2. The precise meaning of “gauche effects” and “1,3-diaxial interaction”

In our analysis, the definition of *gauche* effect is clear and straightforward. It is  $(G_{o,o} - G_{a,a})$  and it is negative since  $PE_{12}$  is negative. Therefore the absolute value of our *gauche* effect is  $(G_{a,a} - G_{o,o})$ . Similarly, the 1,3-diaxial effect is clearly defined in our analysis by  $(E_{o,o} - E_{a,a})$ . These terms are related to the *gauche* effect (1.8 kcal/mol) and the 1,3-diaxial interaction (2.3 kcal/mol) determined by RPB as follows. The *gauche* effect defined by RPB is  $2 \times PE_1 - PE_2$ , which in the terms

<sup>c</sup>Considering the complexity of the evaluation of three-body effects, it would not seem feasible or economic to apply a similar additivity method to the calculation of conformational preference energies for larger or more complicated compounds.

<sup>d</sup>There are two exceptions in that  $\Delta(\mathbf{5})$  computed at MP2/6-31G\* is 0.8 kcal/mol and  $\Delta(\mathbf{12})$  computed at MP2/6-311+G\*\* is 0.9 kcal/mol. Most likely, these differences are due to errors in the term evaluation, rounding problems etc.

of our analysis equals

$$\begin{aligned} \text{gauche effect} = 2 \times PE_1 - PE_2 &= (G_{a,a} - G_{o,o}) + 2 \times (G_{o,H} - G_{a,H}) \\ &\quad - 2 \times (T_{a,H} - T_{o,H}) - (T_{a,a} - T_{o,o}). \end{aligned} \quad (9)$$

The 1,3-diaxial interaction defined by RPB is  $2 \times PE_1 - PE_3$  which can be expressed in our terms as

$$1, 3\text{-diaxial} = 2 \times PE_1 - PE_3 = (E_{o,o} - E_{a,a}) + 2 \times (E_{a,H} - E_{o,H}). \quad (10)$$

These relations reveal that RPB's *gauche* effect includes 1,2-alkoxy-hydrogen and 1,2-alkyl-hydrogen-*gauche* interactions as well as 1,2-*trans* interactions ( $T_{a,H} - T_{o,H}$ ) and  $(T_{a,H} - T_{o,H})$ . Furthermore, it can be seen that the RPB definition of the 1,3-diaxial interaction  $(E_{a,a} - E_{o,o})^e$  also includes 1,3-alkyl-hydrogen and 1,3-alkoxy-hydrogen interactions.

RPB's  $PE_{12}$  is a sum of six *gauche* and six 1,3-diaxial interactions

$$PE_{12} = 6 \times \text{gauche effect} + 6 \times 1, 3\text{-diaxial effect}, \quad (11)$$

and the comparison with Eq. (2) results in the condition:

$$\begin{aligned} 0 &= 6 \times [2 \times (G_{o,H} - G_{a,H}) - 2 \times (T_{a,H} - T_{o,H}) - (T_{a,a} - T_{o,o})] \\ &\quad + 6 \times [2 \times (E_{a,H} - E_{o,H})] - 6 \times (T_{a,a} - T_{o,o}) \\ 0 &= (G_{o,H} - G_{a,H}) - (T_{a,H} - T_{o,H}) - (T_{a,a} - T_{o,o}) + (E_{a,H} - E_{o,H}). \end{aligned}$$

For the RPB approach to work, this condition has to hold. RPB neglect the  $T$  terms altogether and rely on the condition  $0 = (G_{o,H} - G_{a,H}) + (E_{a,H} - E_{o,H})$ . One can hope for cancellation but there is no reason why there should be a strict cancellation. More realistically, one might assume that this condition holds approximately because  $(G_{o,H} - G_{a,H})$ ,  $(E_{a,H} - E_{o,H})$ ,  $(T_{a,H} - T_{o,H})$ , and  $(T_{a,a} - T_{o,o})$  presumably all are small. We pointed out above that most  $\Delta$  values are rather small and that finding suggests that indeed this approximation works well in most cases. In our method, there is no need to attach values to any of the pair-wise interactions because the formalism does not rely on the evaluation of a test function (Fig. 1).

#### 4. Conclusion

It is a direct conclusion of our discussion that the conformational preference energy of **12** is the result of the *transferability* and *additivity* of the 1,2- and the 1,3-interactions. These interactions cause all of the conformational preference energies of **1**, **2**, **3**, and **12**. Our analysis clearly demonstrates that the 22 kcal/mol energy preference of the *O*-equatorial conformation of **12** over the *O*-axial conformation can be explained by consideration of the concept of the *gauche* effect and the concept of 1,3-diaxial interactions. The essence of the present work is a

<sup>e</sup>Note that the absolute value of  $E_{a,a} - E_{o,o}$  is  $E_{o,o} - E_{a,a}$  and since RPB makes all the values positive, one can consider our definition of 1,3-diaxial interaction to be  $E_{o,o} - E_{a,a}$ .



more concise grasp of the concepts “*gauche* effect” and “1,3-diaxial interaction”. We defined all the interaction terms clearly, strict, and exclusive so that they *do not* contain multiple interactions which are neither obvious nor intuitive.

We presented a more systematic and conceptually clear approach to analyze conformational effects of **4–12**. This approach is compound-independent and the analysis of the spiro(THF)cyclohexanes leads to a more generalized hypothesis: the conformational preference energy of multi-substituted cyclohexanes is *additive* in terms of the conformational preference energy of less substituted compounds, which contain all the possible interactions existing in the multi-substituted cyclohexane in question. Certainly it is impossible to exhaust all the multi-substituted cyclohexanes. But it is obviously true that all the possible interactions in any multi-substituted cyclohexane exist in less substituted cyclohexanes simply because we can keep just the two groups involved in an interaction and leave off any other substituents. The only exceptions are the bi-substituted cyclohexanes since mono-substituted cyclohexanes do not contain any 1,2-, 1,3-, or 1,4-interactions between *two* substituents. This hypothesis is open for testing by future experimental and computational studies.

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