

# A quantitative model for alkane nucleophilicity based on C-H bond structural/topological descriptors

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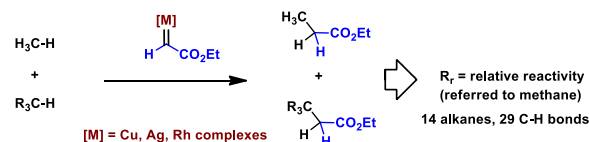
**Abstract:** A first a quantitative model for the calculations of the nucleophilicity of alkanes is described. A statistical treatment is applied to the analysis of the reactivity of twenty-nine different alkane C-H bonds toward *in situ* generated metal-carbene electrophiles. The correlation of the recently reported experimental reactivity with two different sets of descriptors comprising a total of 86 parameters is studied, resulting in the Quantitative DDescriptor-based Alkane Nucleophilicity (QDEAN) model. This model consists of an equation with only six structural/topological descriptors, and that reproduces the relative reactivity of the alkane C-H bonds. This reactivity can be calculated from parameters emerging from the schematic drawing of the alkane and a simple set of sums.

The application of statistical techniques to the understanding of chemical problems is emerging as a powerful tool for the prediction of chemical behavior.<sup>[1,2,3,4,5,6]</sup> Two main approaches are employed depending on the nature of the descriptors used. On the one hand, general descriptors, not directly related to the specific problem evaluated, are employed in free-energy relationships of widespread use in physical organic chemistry, such as QSAR methods or the Hammett equation. In this context, Sigman has described reaction-oriented descriptors for several organic transformations.<sup>[7,8]</sup> On the other hand, Aires took advantage of statistical techniques to estimate bond dissociation energies (BDEs) for a number of organic molecules,<sup>[9]</sup> whereas Jensen and Alsborg automated the design of organometallic molecules.<sup>[10,11]</sup> Predictive modeling has also been provided by Rothenberg,<sup>[12,13,14]</sup> Bo<sup>[15,16]</sup> and Paton,<sup>[17]</sup> while one of our groups, among others, has used multivariate

regressions to find free-energy relationships between BDEs in organometallic chemistry.<sup>[18,19,20,21]</sup>

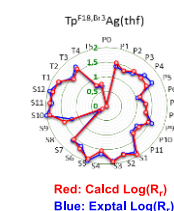
The alternative approach consists in the generation of new, problem-specific descriptors from statistical procedures. Fey applied<sup>[22,23]</sup> principal component analysis (PCA) to define new descriptors and generate a database for ligand knowledge. Some of us have successfully used singular value decomposition (SVD) in the search for somewhat hidden descriptors governing the metal-ligand BDEs.<sup>[24]</sup> New descriptors may also be generated by machine-learning techniques.<sup>[25,26,27,28,29]</sup>

Previous work



This work

- Statistical treatment of above  $R_r$  scale  
- Experimental values can be fitted with just six topological descriptors of the C-H bond



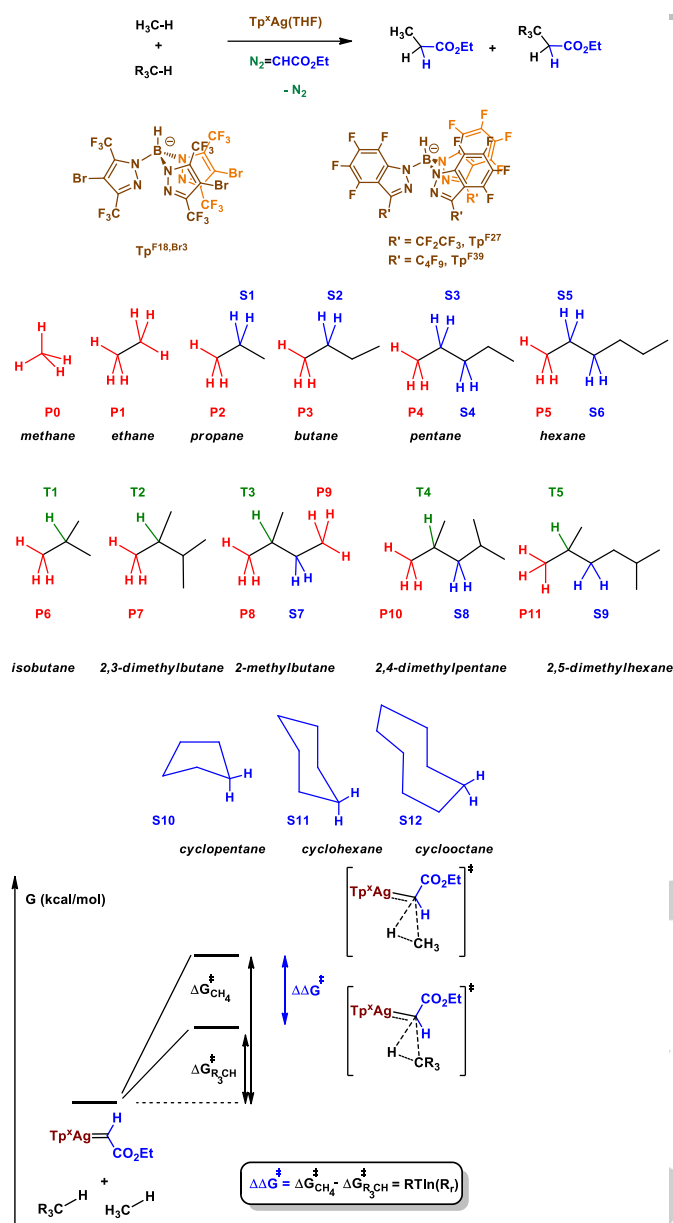
**Scheme 1.** The previously reported first quantitative scale of nucleophilicity of alkanes has been statistically studied and fitted (radial plot) using six topologic descriptors of the evaluated C-H bond.

Our groups have recently described the first experimental scale of relative reactivity of the carbon hydrogen-bonds of alkanes,<sup>[30]</sup> with methane as the reference, toward metal-carbene species as organometallic electrophiles. In this article we report the statistical treatment of that nucleophilic scale of alkanes, which has led to the development of a model that replicates the experimental data at a very high extent by using structural characteristics of those C-H bonds. Our aim is to find a predicting tool for the challenging low reactive C-H bonds of alkanes.

Scheme 2 shows the array of fourteen alkanes previously evaluated by means of competition experiments using silver-based catalysts to promote the catalytic insertion of the carbene  $\text{CHCO}_2\text{Et}$  from ethyl diazoacetate ( $\text{N}_2\text{CHCO}_2\text{Et}$ ) into those 29 C-H bonds. The relative reactivity ( $R_r$ ) was obtained with methane as the reference, although the use of  $\log(R_r)$  seems more appropriate since it can be correlated with  $\Delta\Delta G^\ddagger$  values: this is the difference of free energy in the step where the selectivity is decided, *i. e.*, the interaction of the electrophilic metalcarbene intermediate with the nucleophilic C-H bond (Scheme 2).

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**Scheme 2.** Top: Alkanes and silver catalysts employed in competition studies leading to relative reactivities ( $R_r$ ) of 29 C-H bonds, referred to that of methane. Bottom: The selectivity is decided in the step involving the interaction of a silver-carbene intermediate and the C-H bonds. The  $\Delta\Delta G^\ddagger$  value can be estimated from experimental  $R_r$  values.

We first analyzed the previously reported<sup>[30]</sup> experimental data and explored possible statistical correlations between them with SVD (Singular Value Decomposition), a technique similar to PCA (Principal Component Analysis) that was successfully applied in a previous work to identify hidden descriptors for metal-ligand bond dissociation energies.<sup>[24]</sup> However, this

approach did not yield significant chemical insight for the current system probably due to the lack of diversity in the available sample: C-H bonds behave similarly with all three metal fragments, and data for different complexes thus essentially repeating the same information.

Next, we evaluated the performance of standard molecular descriptors through a series of simple and multiple linear regressions, in a treatment similar to that of the QSPR or QSAR methods.<sup>[31]</sup> We computed the correlation between the reactivity of a given C-H bond and a series of descriptors associated to this bond. We chose 66 different parameters as descriptors, including orbital energies, atomic charges, and other parameters of the alkanes (R-H) and related species such as the R· radical resulting from H abstraction. The full list of the 66 descriptors is presented in the Supporting Information (SI). This treatment was applied to the relative reactivity of each C-H bond to methane with the three different silver catalysts as shown in Scheme 2. We found that the simple and multiple linear regressions between our set of computational descriptors and the experimental data showed only mild correlations. We will discuss here only the results for the  $\text{Tp}^{\text{F18,Br3}}\text{Ag(THF)}$  catalyst. When using one descriptor, the best correlation with the experimental  $\log(R_r)$  is very low ( $r^2 = 0.381$ ). Correlation improves upon increasing the number of descriptors with  $r^2$  values of 0.540, 0.680, 0.818, 0.860 and 0.933 for two, three, four, five and six descriptors, respectively. Albeit a value of 0.933 could be considered acceptable, the descriptors involved are far from being easily interpreted, as there are descriptors that are heavily correlated with each other, for example two BDEs involving different types of cleavages. The achievement of high  $r^2$  seems to be associated to over-parametrization, and formulation of a chemically useful interpretation from this analysis is dubious.

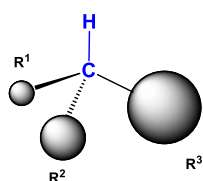
Since we could not obtain significant correlations with conventional descriptors, we decided use of very simple structural/topological descriptors. Molecular graphs have been recently used with success for predicting bond dissociation enthalpies.<sup>[32]</sup> We obtained good results using twenty descriptors that did not require of any electronic structure calculation in their definition. On the contrary, they refer to readily accessible information such as the number of carbons in each chain connected to the C-H bond or the number of non-hydrogen substituents in  $\alpha$ ,  $\beta$  or  $\gamma$  positions, (see the SI for the full list). We then ran a multivariate data analysis similar to that described above for the standard molecular descriptors, and achieved better correlations. The best  $r^2$  values corresponding to one, two, three, four, five and six descriptors were 0.587, 0.799, 0.923, 0.933, 0.943 and 0.953, respectively. Although one could argue that a good agreement was already reached with three descriptors, this had the drawback of not discriminating between some of the C-H bonds under consideration, which would have identical values for the three descriptors.

We finally settled on the six descriptors  $D$  shown in Scheme 3, which seemed to be somewhat more intuitive, a set that provides a  $r^2$  value of 0.936 for reactions with  $\text{Tp}^{\text{F18,Br3}}\text{Ag}(\text{THF})$  as the silver carbene precursor.  $D_{\text{Ctype}}$  indicates the type of the *ipso* carbon involved in the C-H bond of interest with values of 1 for primary, 2 for secondary and 3 for tertiary.  $D_{R1}$ ,  $D_{R2}$  and  $D_{R3}$  are three descriptors that indicate the number of carbon atoms in each of the three substituents on the *ipso* carbon.<sup>33</sup> The labels are not random:  $D_{R1}$  corresponds to the substituent with the lowest number of carbons and  $D_{R3}$  to that with the highest

#### Quantitative Descriptor-based Alkane Nucleophilic (QDEAN) Model

$$\log(R_r) = A + C_{\text{Ctype}}D_{\text{Ctype}} + \sum(C_{Ri} \times D_{Ri}) + C_{\beta}D_{\beta} + C_{\text{st}}D_{\text{st}}$$

#### Descriptors



- $D_{\text{Ctype}}$  degree of substitution (1, 2 or 3)  
 $D_{Ri}$  number of carbons in  $R_i$  ( $R^1$ ,  $R^2$  and  $R^3$ )  
 must follow  $D_{R1} < D_{R2} < D_{R3}$   
 $D_{\beta}$  number of Me groups in  $C_{\beta}$  (in three  $R_i$ )  
 $D_{\text{st}}$  the steric factor (1 or 0)



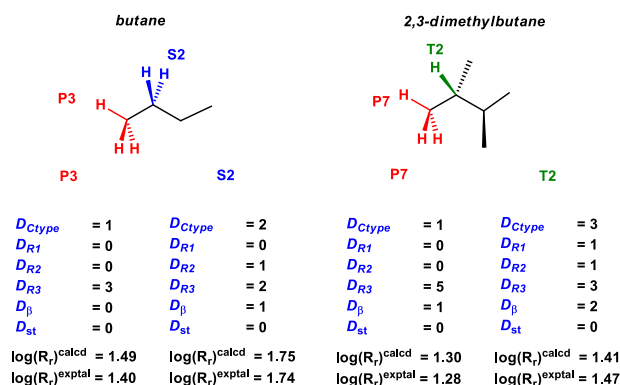
	$\text{Tp}^{\text{F18,Br3}}\text{Ag}(\text{THF})$	$\text{Tp}^{\text{F27}}\text{Ag}(\text{THF})$	$\text{Tp}^{\text{F39}}\text{Ag}(\text{THF})$
$A$	1.053	1.174	1.162
$C_{\text{Ctype}}$	0.467	0.375	0.435
$C_{R1}$	-0.626	-0.542	-0.572
$C_{R2}$	-0.040	-0.001	-0.015
$C_{R3}$	-0.009	-0.016	-0.010
$C_{\beta}$	-0.176	-0.195	-0.212
$C_{\text{st}}$	-0.972	-0.969	-1.005
$r^2$	0.936	0.920	0.942
Max error	0.261	0.296	0.186
Mean error	0.084	0.095	0.089

**Scheme 3.** The equation, descriptors ( $D$ ), coefficients ( $C$ ) correlation indexes and associated errors to predict the relative reactivity of the C-H bond of alkanes in the transformation shown in Scheme 2.

number.  $D_{\beta}$  is the number of methyl groups in a  $\beta$  position with respect to the C-H bond of interest.  $D_{\text{st}}$  is a binary term (0 or 1) that we had to introduce to account for three particular cases (S8, T4, T5, labels in Scheme 2) that seemed highly hindered (the label "st" stands for steric). It is worth mentioning at this stage that the seeming arbitrariness in the choice of the significant descriptors is mostly decided by the statistical procedure. The number of methyl groups in  $\beta$  is important, but the procedure also allowed a role for those in the  $\gamma$  carbon (two C-C bonds away), which happen to be irrelevant. Seemingly, the steric term appears in specific cases, but has always the same value. Further work will be necessary to predict in which cases this steric term is necessary.

The regression formulas used in the statistical analysis can be rearranged to produce an equation for the estimation of  $\log(R_r)$  (Scheme 3), which can in this way be expressed as the sum of

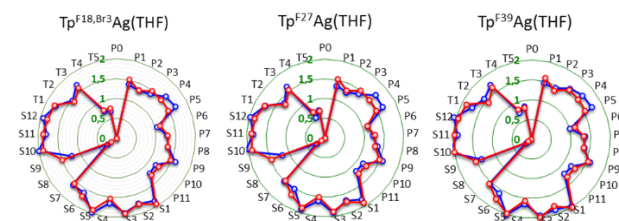
seven terms: one independent term ( $A$ ) and six descriptors  $D_i$ , each of them weighed by a coefficient  $C_i$ , in this Quantitative Descriptor-based Alkane Nucleophilicity (QDEAN) Model.



**Figure 1.** Experimental and QDEAN calculated  $\log(R_r)$  values for butane and 2,3-dimethylbutane using  $\text{Tp}^{\text{F18,Br3}}\text{Ag}(\text{THF})$  as the silver carbene precursor.

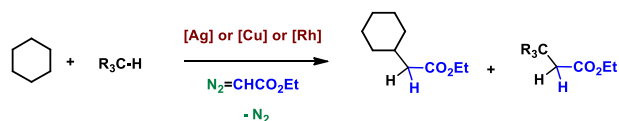
Application of the same treatment to the experimental results with the other two silver complexes provides correlation indices  $r^2$  of 0.920 and 0.942 for the  $\text{Tp}^{\text{F27}}\text{Ag}$ - and  $\text{Tp}^{\text{F39}}\text{Ag}$ -based systems, respectively. The associated coefficients for the predictive equation are shown in Scheme 3. The results for the three silver systems are too similar to each other to discuss possible differences between them. Figure 1 illustrates the application of QDEAN to calculate the value of  $\log(R_r)$  for the C-H bonds of two different hydrocarbons, namely butane and 2,3-dimethylbutane, by using  $\text{Tp}^{\text{F18,Br3}}\text{Ag}(\text{THF})$  as the silver carbene precursor.

When the procedure is applied to all the 29 C-H bonds shown in Scheme 2 and the three metallocarbene precursors, an immediate comparison between the experimental and calculated sets of data can be readily made using radial plots (Figure 2) that show that the calculated  $\log(R_r)$  values are in very good agreement with the experimental ones. To the best of our knowledge, *this is the first approach to a quantitative modeling of the reactivity of non-activated hydrocarbon C-H bonds towards electrophiles*. We believe that this model is quite remarkable since it provides a good correlation despite employing quite simple parameters.



**Figure 2.** Radial plots comparing the experimental (blue) and QDEAN-estimated (red) values for  $\log(R_r)$  for the alkanes shown in Scheme 2.

In order to expand these studies to other metals, copper- and rhodium-carbene electrophiles were generated in situ by using

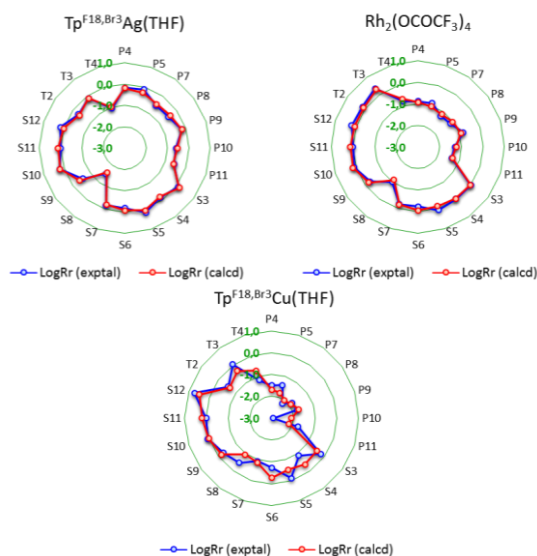


$$[\text{Ag}] = \text{Tp}^{\text{F}18,\text{Br}3}\text{Ag}(\text{THF}) \quad (\text{Tp}^{\text{X}} = \text{Tp}^{\text{F}18,\text{Br}3}, \text{Tp}^{\text{F}27}, \text{Tp}^{\text{F}39})$$

$$[\text{Cu}] = \text{Tp}^{\text{F}18,\text{Br}3}\text{Cu}(\text{THF})$$

$$[\text{Rh}] = \text{Rh}_2(\text{OCOCF}_3)_4$$

$$\log(R_r) = A + C_{\text{Ctype}}D_{\text{Ctype}} + \sum(C_{\text{Ri}} \times D_{\text{Ri}}) + C_{\beta}D_{\beta} + C_{\text{st}}D_{\text{st}}$$



**Scheme 4.** Radial plots obtained after applying QDEAN to the data from competition reactions with liquid alkanes and the series of silver, copper and rhodium carbene electrophiles.

$\text{Rh}_2(\text{OCOCF}_3)_4$  and  $\text{Tp}^{\text{F}18,\text{Br}3}\text{Cu}(\text{THF})$ . However, they cannot induce the functionalization of the C-H bond of methane and the gaseous alkanes, unlike the silver-based electrophiles. Therefore, the relative reactivity studies were carried out with a second set of only 20 C-H bonds, excluding those of the  $\text{C}_1\text{-C}_4$  alkanes.<sup>[30]</sup> Cyclohexane was employed as the reference, and the electrophiles were generated from ethyl diazoacetate and the aforementioned array of silver, copper and rhodium complexes (Scheme 4). We wondered if QDEAN could also account for the behavior of these additional electrophiles as well as for the change in the C-H bond reference. To our delight, we found that *the same descriptors, equation and rules shown in Scheme 3 give a good description for these additional sets of data.* This is clear from the radial plots shown in Scheme 4, where estimated data (in red) are close to experimental data (in blue), even though the overall behavior is different for silver, rhodium and copper complexes.

The coefficients associated to each of the systems are presented in Table 1. Comparison with the data above for the other set of experiments shows the strengths and limitations of our model. We are fitting six coefficients with only twenty experimental points, which gives much more statistical deviation than when using twenty-nine experimental points. The availability of a larger number of experimental data seems thus critical for increased accuracy. The coefficients for the rhodium and copper systems are in any case clearly separated from those of the silver systems. Our model is therefore also able to discriminate between the electrophiles reacting with alkanes.

In conclusion, we have applied statistical techniques to analyze the relative reactivity ( $R_r$ ) of twenty-nine carbon-hydrogen bonds of fourteen alkanes in their reaction with *in situ*

**Table 1.** Coefficients, correlation index, and associated errors associated to the application of QDEAN to the five complexes with cyclohexane-based experimental data.

	$\text{Tp}^{\text{F}18,\text{Br}3}\text{Ag}$	$\text{Tp}^{\text{F}27}\text{Ag}$	$\text{Tp}^{\text{F}39}\text{Ag}$	$[\text{Rh}_2]$	$\text{Tp}^{\text{F}18,\text{Br}3}\text{Cu}$
A	-0.209	0.042	-0.176	-1.256	-2.122
$C_{\text{Ctype}}$	0.323	0.186	0.236	0.764	0.777
$C_{\text{R}1}$	-0.485	-0.396	-0.295	-0.480	-0.540
$C_{\text{R}2}$	-0.048	-0.016	0.004	0.049	0.392
$C_{\text{R}3}$	-0.076	-0.110	-0.079	-0.107	-0.087
$C_{\beta}$	-0.190	-0.206	-0.208	-0.095	-0.212
$C_{\text{st}}$	-0.893	-0.905	-1.017	-0.828	-0.428
$r^2$	0.952	0.949	0.965	0.962	0.842
Max error	0.178	0.185	0.179	0.194	0.839
Mean error	0.076	0.084	0.072	0.093	0.290

generated electrophilic metal-carbene complexes. After trying different sets of descriptors, the best results are obtained with a group of six topological descriptors. The resulting Quantitative DEscriptor-based Alkane Nucleophilicity (QDEAN) provides a good fitting between the calculated and the experimental data. The model works with five different metal-carbene complexes, three of them containing silver, the other two rhodium and copper. The set of descriptors is always the same, whilst the coefficients in the equation are specific for each electrophile. This study constitutes the starting point for further developments that can lead to a better understanding of the nature of the alkane C-H bond reactivity and, ultimately, to improving their use as raw materials in chemical synthesis.

## Acknowledgements

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**Keywords:** reactivity model Alkanes descriptors C-H functionalization nucleophilicity

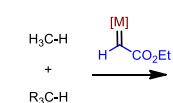
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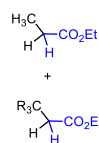
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- [33] The chain length descriptors will likely have a saturation value from where further increases have no effect, but we could not estimate it from our set of data.

## Alkane reactivity

The QDEAN Model constitutes the first approach to a quantitative modelling of the reactivity of alkane C-H bonds towards electrophiles is reported. A remarkable correlation between experimental and calculated values is achieved with just six topological descriptors based on the C-H bonds under evaluation.



[M] = Cu, Ag, Rh complexes  
14 alkanes, 29 C-H bonds

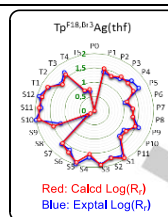


$R_r$  = relative reactivity  
(referred to methane)

Q-DEAN



statistical analysis  
six topological descriptors



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**A quantitative model for  
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