ABSTRACT: The use of computed interaction energies and distances as parameters in multivariate correlations is introduced for postulating non-covalent interactions. This new class of descriptors affords multivariate correlations for two diverse catalytic systems with unique non-covalent interactions at the heart of each process. The presented methodology is validated by directly connecting the non-covalent interactions defined through empirical data set analyses to the computationally derived transition states.

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Parametrization of Non-covalent Interactions for Transition State Interrogation Applied to Asymmetric Catalysis
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Supporting Information

Figure 1. Computed energies ER and distances DR as parameters. (A) General idea and π−π interactions (Figure 1A,B). In particular, DR is dependent on both distinct geometric and electronic features, since it is influenced by the attractive energy as well as the substituent size. Moreover, when an NCI can occur in more than one conformer, the associated properties can be weighted according to their energies, as depicted in Figure 1C; the obtained parameters are represented as ERw and DRw. For the two case studies presented below, the relevant complexes were calculated at the B97-D/def2TZVP level of theory, since this functional paired with a triple-ζ basis set has been reported to be a practical, economical compromise for computing NCIs.

In order to test our hypothesis, we examined the kinetic resolution of chiral benzylic alcohols reported by Birman and co-workers (Figure 2A), in which π stacking was demonstrated to be a controlling element in the computed TSs (Figure 2B). In addition, sufficient data spanning a significant range of measured displaced arene dimers (Figure 1A), which linearly correlate with the Hammet σp parameter. These reports inspired us to compute representative interaction energies (ER) and distances (DR, defined as the distance between the centers of the two interacting moieties) to be used as descriptors for putative π interactions (Figure 1A,B). In particular, DR is dependent on both distinct geometric and electronic features, since it is influenced by the attractive energy as well as the substituent size. Moreover, when an NCI can occur in more than one conformer, the associated properties can be weighted according to their energies, as depicted in Figure 1C; the obtained parameters are represented as ERw and DRw. For the two case studies presented below, the relevant complexes were calculated at the B97-D/def2TZVP level of theory, since this functional paired with a triple-ζ basis set has been reported to be a practical, economical compromise for computing NCIs.

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In order to test our hypothesis, we examined the kinetic resolution of chiral benzylic alcohols reported by Birman and co-workers (Figure 2A), in which π stacking was demonstrated to be a controlling element in the computed TSs (Figure 2B). In addition, sufficient data spanning a significant range of measured
selectivity factors ($s$ from 6 to 117, $\Delta \Delta G^\ddagger$ from 0.97 to 2.58 kcal/mol) were reported, which is required for developing statistically sound models (see the Supporting Information (SI) for details).\textsuperscript{15,16} Parameter collection was initiated by computing 28 unique $\pi-\pi$ sandwich complexes between the aryl/alkenyl groups and model systems 1 and 2, which represent the cationic acylated catalysts 3 and 4 used in the reaction (Figure 2C). To simulate a $\pi$-stacking interaction, the two arenes were aligned in a parallel orientation at a defined distance, centering the interacting arene with the pyridinium ring in 1 or 2. Subsequently, the distance between the rings was optimized, resulting in the minimum energy for the stacked conformation, $^3 \text{En}_\pi$ at distance $^3 \text{D}r_{\pi}$ (Figures 2D and SIA). When additional conformers were possible, the formula in Figure 1C was applied, affording $^3 \text{En}_\pi$ and $^3 \text{D}r_{\pi}$ as weighted parameters to account for the possibility of dynamic interactions (see the SI).

Initial evaluation of these parameters revealed a single-parameter correlation between $^3 \text{D}r_{\pi}$ and the selectivity factor $s$, represented as the $\Delta \Delta G^\ddagger$ value ($R^2 = 0.70$; Figure S4), which supports the presence of a stacked $\pi-\pi$ interaction in the TS. After application of MLR to interrogate additional effects on the reaction’s selectivity, the model reported in Figure 2D was identified ($R^2 = 0.92$), effectively describing 28 data points with three additional terms: the Sterimol parameters $^3 \text{B}_{1,\text{Alk}}$ (alkyl substituent’s minimum width) and $^3 \text{B}_{5,\text{Ar}}$ (aryl substituent maximum width) and the cross term $^3 \text{D}r_{\pi} \cdot ^3 \text{En}_\pi$. Cross-validation methods are consistent with a statistically sound model (see the leave-K-out (LKO) values). Examination of each term’s coefficient in the model suggests that the reaction’s enantioselectivity is most influenced by the $\pi$-stacking interaction (represented by the terms $^3 \text{D}r_{\pi}$ and $^3 \text{D}r_{\pi} \cdot ^3 \text{En}_\pi$) followed by steric effects, consistent with previous studies.\textsuperscript{16}

After evaluating our new $\pi$ parameters for mechanistic rationalization of a well-studied reaction, we sought to test whether they can also be applied to a system for which the specific interactions occurring in the TS have not yet been determined. Hence, the second case study for the application of these $\pi$ parameters was the enantiodivergent fluorination of allylic alcohols previously reported by our teams (Figure 3A).\textsuperscript{17} In this process, the allylic alcohol and the boronic acid (BA) condense to form a mixed boronic ester, which is proposed to coordinate via H-bonding with the chiral phosphate anion (PA).\textsuperscript{17b} From this complex, the enantioselective electrophilic fluorination occurs. Notably, the enantioselectivity ranges from $-92$ to $+90\%$ ee when various combinations of PAs and BAs are applied, reflecting a $\Delta \Delta G^\ddagger$ range of 3.5 kcal/mol. Thus, this reaction is highly sensitive to NCIs involved in enantioselectivity-controlling events. Despite extensive mechanistic studies that provide support for the general reaction mechanism,\textsuperscript{17b} a clear representation of the likely NCIs responsible for the enantioselectivity has not been elucidated. In this context, previous attempts to correlate all of the measured enantioselectivities through MLR were unsuccessful.

Two key observations provided a framework to initiate interrogation of this system: (1) meta-substituted BAs lead to inverted enantioselectivity compared with other substitution patterns on the BA, and (2) the sensitivity toward the BA substitutions is amplified when PAs and BAs are applied, reflecting a $\Delta \Delta G^\ddagger$ range of 3.5 kcal/mol. Thus, this reaction is highly sensitive to NCIs involved in enantioselectivity-controlling events. Despite extensive mechanistic studies that provide support for the general reaction mechanism,\textsuperscript{17b} a clear representation of the likely NCIs responsible for the enantioselectivity has not been elucidated. In this context, previous attempts to correlate all of the measured enantioselectivities through MLR were unsuccessful.

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catalysts, such as IR stretching frequencies and Sterimol values, were acquired using a simple model system (Figure 3B; see the SI). The parameters include $^1D\pi_{\text{ba}}$, accounting for geometric requirements derived from the apparent presence of a $\pi$ interaction; $B_{\text{ba}}$ and $L_{\text{pa}}$. Sterimol values describing steric effects from BA and the catalyst, respectively; and, $\rho_{\text{POsy}}$, the phosphate symmetric stretching intensity, which may represent the ability of each PA to engage in H-bonding/electrostatic interactions. Since previous attempts to model this entire data set were unsuccessful, these new NCI parameters provided the missing information for describing key interactions in this complex reaction. More importantly, these results suggest that these parameters may provide a powerful platform for uncovering subtle NCIs, even when limited mechanistic/structural knowledge is available.

In order to further leverage this statistical physical organic strategy, a computational TS analysis for this reaction was performed at the $\omega$B97X-D/def2-TZVPP/SMD(toluene) level of theory on the $\omega$B97X-D/6-31G(d) geometries. Nonrelevant hydrogen atoms have been omitted for clarity.

![Figure 4. Structures and relative free energies (in kcal/mol) of the low-lying TSs for (A) PA 6/4-MePhB(OH)$_2$ and (B) PA 6/3,5-(MeO)$_2$PhB(OH)$_2$. Energies were computed at the $\omega$B97X-D/def2-TZVPP/SMD(toluene) level of theory on the $\omega$B97X-D/6-31G(d) geometries. Nonrelevant hydrogen atoms have been omitted for clarity.](image)
the optimized reaction conditions previously reported, in which the best PA catalyst, AdDIP (i.e., 2,6-(iPr)2-4-Ad-Ph), contains an adamantanyl (Ad) group at the para position.\(^7\) Conversely, when a 3,5-unsubstituted BA is used, a 3,5-unsubstituted BA is used, an adamantyl (Ad) group at the para position.\(^7\) Conversely, alkyl moieties, thus stabilizing this conformation and allowing describing NCIs in catalysis prompted us to develop new parameters for further validating the new parameters as descriptors of NCIs occurring in the TS.

In conclusion, the need for new tools to identify and quantify NCIs in catalysis prompted us to develop new parameters for describing \(\pi\) interactions: \(\text{Ex}^\pi\) and \(\text{D}^\pi\). These easily calculated parameters have been tested in two different catalytic systems using multivariate correlations. The obtained information agreed with previously reported studies in Birman’s kinetic resolution of benzyl alcohols by supporting the occurrence of a \(\pi\)-stacking interaction. These parameters also provided detailed insight into a complex reaction, namely, the fluorination of allylic alcohols. Indeed, for this catalytic system the obtained model facilitated the identification of interactions occurring in the computed TSs. Thus, this new class of parameters provides a valuable extension as a complementary strategy to rigorous TS computations, both to developing structure–function relationships by describing weak yet significant interactions occurring in the reaction. As shown, the use of \(\text{Ex}^\pi\) and \(\text{D}^\pi\) in multidimensional analysis offers a broad perspective of a reaction that can be distilled into a mathematical equation, directly relating the parameters to a TS structure. Hence, this methodology offers the opportunity to validate TS analyses through a set of experimental data. We see it as a complementary strategy to rigorous TS computations, both of which inform the nature of potential NCIs. We are currently integrating these approaches in ongoing projects as well as exploring the application of this strategy to other NCIs such as electrostatics and dispersion forces.

**ASSOCIATED CONTENT**

Supporting Information

Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b02311.

Experimental and modeling details, table of parameters, and DFT energies and geometries (PDF)

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**Notes**

The authors declare no competing financial interest.

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