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Proximity Effect: An Insight into the Fundamental Forces Governing Chemical Reactivity of Aromatic Systems

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Pseudopericyclic reaction, ortho effect, DFT

ABSTRACT

The analysis of different layers of proximity-effect in ortho-substituted aromatic compounds, using a DFT level study, is reported. Polar and steric components of the proximity-effect have been partitioned by applying multivariate regression analysis to an unusual six-electron hetero-electrocyclic reaction of the ortho-substituted nitrosostyrenes. The two pathways, 1,5 and 1,6 cyclizations, emanating from these substrates result into zwitterionic five-membered and neutral six-membered rings respectively. The substituents at position-1, which are adjacent to the polar nitroso group, influenced the barrier primarily through electronic effect. Furthermore, a mechanistic shift from 1,5 to 1,6 pathway, for certain substrates, is explained by the electronic repulsion. In contrast to position-1, the substituents on position-4 stereoelectronically interacted

with bulkier alkene moiety. Furthermore, unlike position-1, the position-4 substituted substrates are predicted to give only 1,5 products. A comparison of the two ortho positions with position-2, which is meta to the nitroso and para to the alkene, revealed an intriguing relationship between various electronic factors.

INTRODUCTION

The fundamental forces governing the chemical reactivity of aromatic systems have been an intense area of research since the 20th century. While most of these studies have been directed towards the electronic effects of the meta and the para-substituents of the phenyl ring, the analysis of substituents on the ortho position remains less understood. Because of its proximity to the reaction center, the ortho position, in addition to the electronic effect, can influence the reaction center through hydrogen bonding, chelation, steric and field effects.[1-7] Unfortunately, the individual contribution of these forces varies in different systems; the attempts to explain the chemical reactivities of ortho-substituted compounds, based on generally applicable set of variables, have been unsuccessful. The present study aims to provide a useful theoretical insight into the nature of this effect through a pseudopericyclic rearrangement of substituted nitrosostyrene (Figure 1). This rearrangement has been proposed to be involved in a Pd-catalyzed reductive rearrangement of nitrostyrenes into synthetically and biologically valuable indole derivatives.[8-10] The substrates involved in this rearrangement are unique as they contain two stereoelectronically different ortho-positions; position-1 is adjacent to the polar nitroso group whereas position-4 is adjacent to the non-polar alkene. As a result, the proximity-effect is predicted to be different for the two positions.

Mechanistically, the nature of the ortho substituents can influence the system to adopt either of the two possible modes of cyclization. An unusual five-atom six-electron 1,5 pseudopericyclic reaction engages the 4π electrons of the carbon framework and the in-plane 2ω electrons of the nitrogen.[11-23] The resulting zwitterion rearranges to give the N-hydroxy-indole derivative (Figure 1). Unlike the 1,5 cyclization, an alternate higher energy path involves a classic 6π electrocyclic reaction giving a neutral six-membered heterocyclic ring.[24] Although only π-electrons seem to participate in the 1,6 cyclization, Houk proposed that the nitrogen or oxygen lone pair could be potentially involved as well. For brevity, we will use the designations, 1,5 and 1,6 cyclizations for the five-atom and the six-atom electrocyclizations respectively.

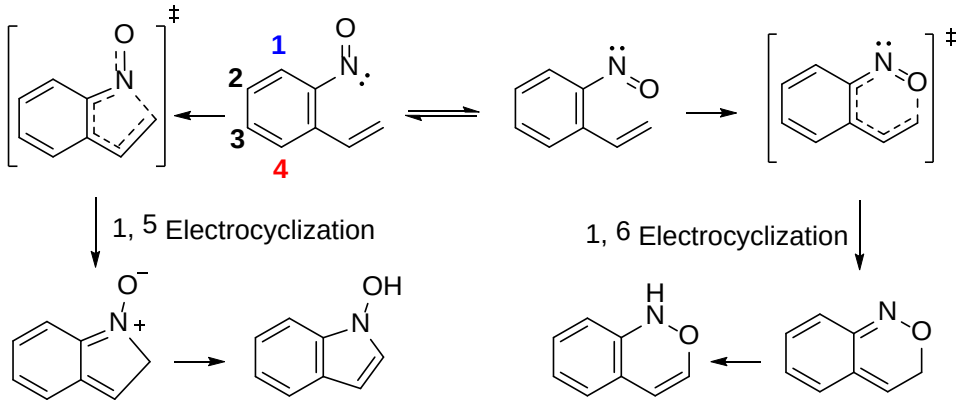

Figure 1. Two pseudopericyclic pathways emanating from nitrososstyrene. The two distinct ortho positions are shown in blue and red colors

RESULTS AND DISCUSSION

In the past, several groups have reported rate acceleration when electron acceptors are placed in proximity to the reaction center.[25-31] In the present study, despite both pathways being concerted, the 1,5 cyclization is expected to proceed via a more polar transition state than the 1,6 pathway. Hence, significant "proximity effect" is anticipated for the 1,5 pathway. To analyze these effects,

a DFT level study was performed using M06-2X functional with 6-311++G(d, p) basis set. This newly introduced method performs very well for the main group thermochemistry, kinetics and non-covalent interactions.[32-38]

Position-1-Ortho Substitution. The substituents on the two ortho positions, 1 and 4 (Figure 1), are expected to exert different degrees of stereoelectronic effect. Substituents on position-1 are predicted to exert a greater degree of electronic effect and more effectively chelate with the nitroso group than on position-4. The calculated barrier for several substituted nitrosostyrenes (X= NO_2, CN, CHO, Br, Cl, F, SH, H, Me, OH, OMe, NH_2, OLi: See SI for the table) showed a low energy 1,5 pathway except for halides and methoxy group which preferred to undergo a 1,6 cyclization instead. The factors influencing 1,6 cyclization were determined using multivariate regression analysis.

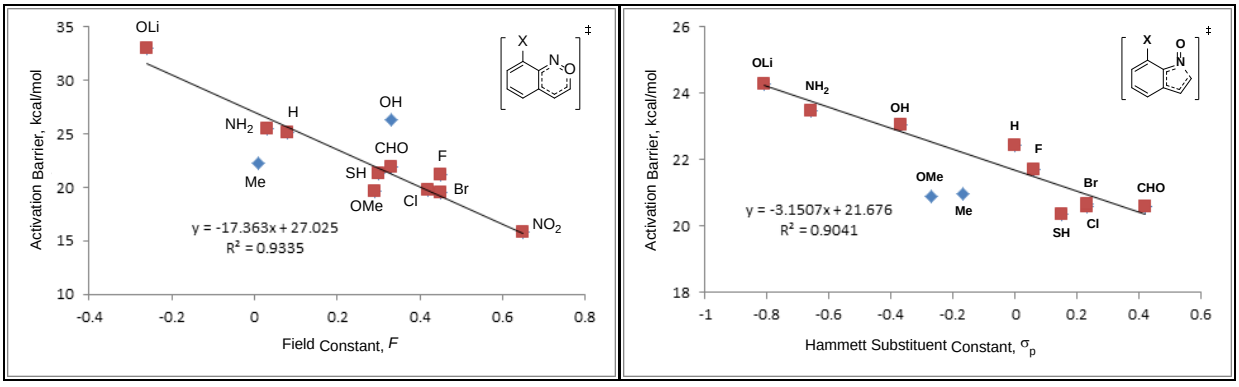

Figure 2. Left: Correlation of modified Swain-Lupton field constants (*F*) with 1, 6 cyclization barrier corresponding to position-1 substituted substrates. Right: Correlation of Hammett constant, σ_p, with the 1, 5 cyclization barrier for position-1 substituted substrates. The activation barriers were calculated using M06-2X functional with 6-311++G(d,p) basis sets

Among several variables studied, such as Hammett substituent constants (σ_v, σ_m, σ_I)[39] and steric constants (E_S and M_r),[40-49] a strong correlation between the activation barrier (Ea) and the field constant (*F*) was observed for the 1,6 cyclization (Figure 2).[50-52] In accordance with the

literature, a negative slope, indicating a lower barrier for the electron withdrawing groups and higher barrier for the electron donating groups, was obtained. However, there were two exceptions to this trend, the hydroxyl, which showed an unusually higher barrier, and the methyl group, which showed a lower barrier than predicted by the correlation plot. A further dissection of TS-geometries revealed an interesting correlation between dihedral angle of the 1,6-TS-ring and the activation barrier. The groups which caused highest distortion also showed the lowest barrier (Figure 3). For most of the groups, the field effect is predicted to cause the extent of distortion whereas the methyl group, which too obeyed this correlation and does not exert significant field effect, interacts sterically with the ortho-nitroso group.

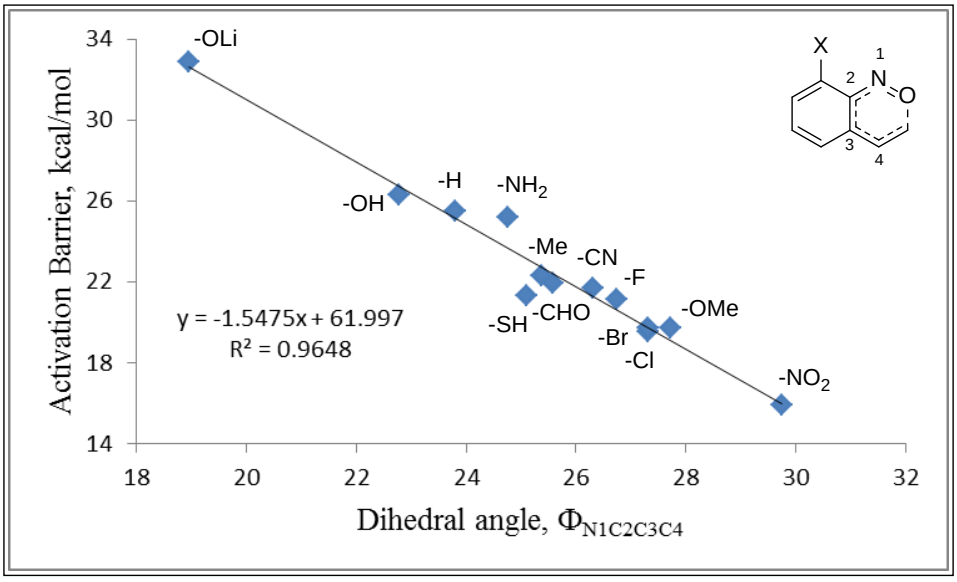

Figure 3. Correlation of activation barrier and dihedral angle, ΦN1C2C3C4. The geometries were optimized using M06-2X /6-311++G(d,p).

Further, in case of the hydroxyl group, a hydrogen bond plays a dual role. On one hand, the hydroxyl group stabilizes the reactant by ~6 kcal/mol more than the corresponding transition state (Figure 4) thereby raising the barrier.[53] On the other hand, the hydrogen bond that stabilizes

the TS, also tries to impose a planar-type TS-geometry (ΦN1C2C3C4: 22.79). The net result is an expectedly higher barrier.

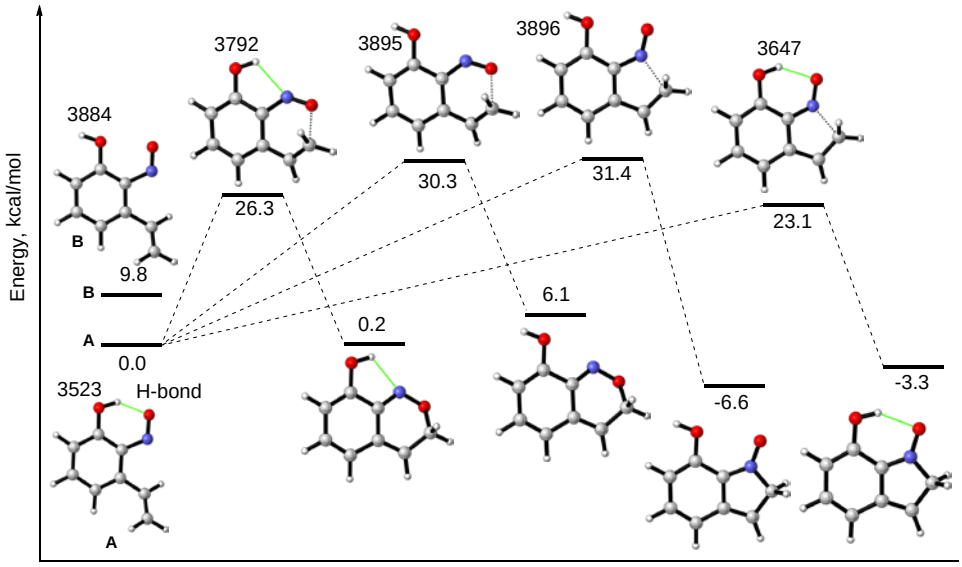

Figure 4. Role of hydrogen bonding in stabilizing the reactant and the transition state of 1,5 and 1,6 cyclization paths when X=OH at position-1. Calculated -OH IR stretching frequencies are given near the hydroxyl group. The activation barriers were calculated using M06-2X functional with 6-311++G(d,p) basis sets.

In contrast to the 1,6 cyclization, the activation barrier of the more polar transition state of the 1,5 path correlates well with the Hammett substituent constants (σ_p). The methoxy and methyl groups (bottom plot, Figure 2) are exceptions to the given trend. Furthermore, unlike what was observed in the 1,6 path, the difference between reactant and transition state stabilization, due to hydrogen bonding in case of hydroxyl group, was found to be only 1.6 kcal.

Interestingly, ortho-halo and ortho-methoxy substrates, the proximity effect which emanates from the electronic repulsion between the groups containing lone pairs and the developing negative charge on the oxygen of the nitroso group in 1,5 cyclization, shifts the course of reaction in favor of 1,6 cyclization. The molecular electrostatic potential (MEP) surfaces of the transition states in these substrates further corroborate this hypothesis (Figure 4). The intense red

color indicates the zone of highest electron density, the lowest electrostatic potential energy and the highest electronic repulsion whereas the blue color depicts otherwise. Furthermore, the proximity effect is also responsible for the difference between 1,5 and 1,6 barrier among halogens. The bromide with bigger 4p orbitals reach closer to the nitroso group causing greater repulsion and hence show the larger difference (1.1 kcal/mol) than the smaller 2p orbitals in fluoride that shows difference of 0.6 kcal/mol.

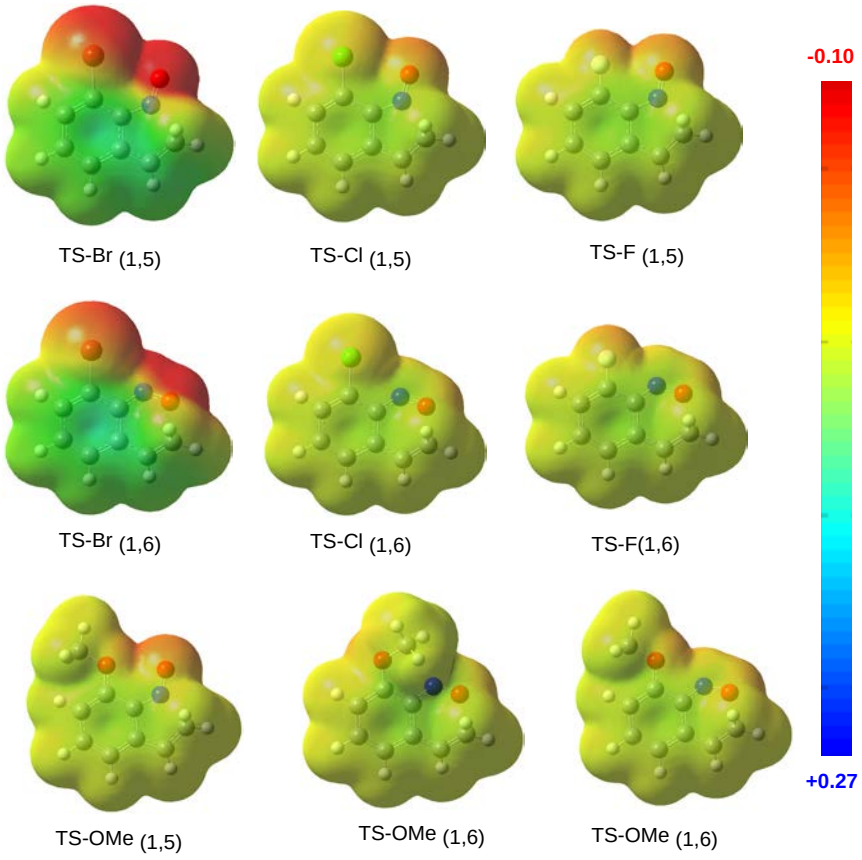

Figure 5. Molecular electrostatic potential (MEP) surface of transition states corresponding to 1,5 and 1,6 electrocyclization of ortho-halo and ortho-methoxy substrates are shown. Geometries were optimized at the M06-2X/6-311++G(d,p) level.

Position-4-Ortho Substitution. Next, we analyzed the impact of substituents on position-4. Unlike position-1, substituents on position-4 drive the reaction through a 1,5 pathway. A strong correlation between the barriers suggested that the same set of parameters affect both pathways (Figure 6).

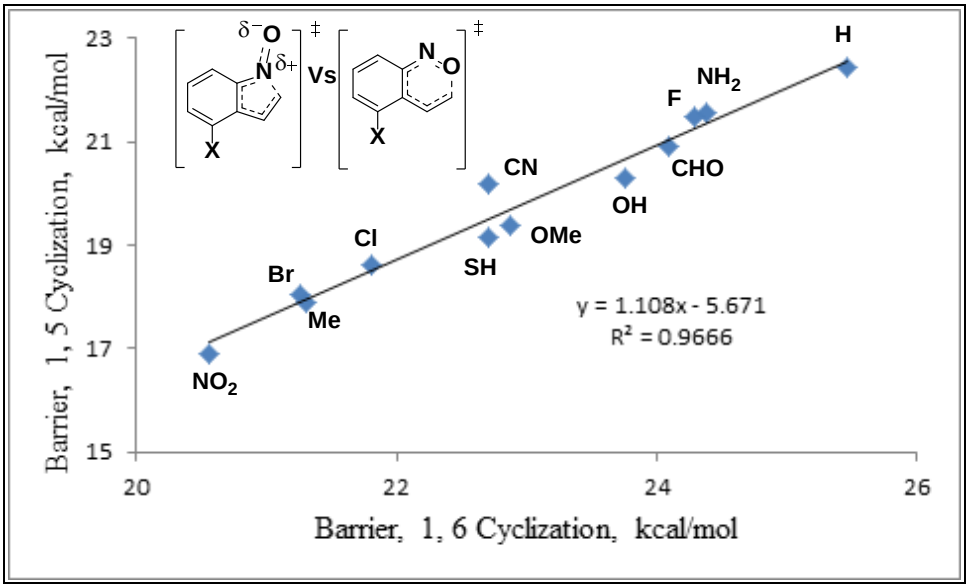

Figure 6. Correlation of 1,5 and 1,6 cyclization barriers for position-4 substituted substrates. The activation barriers were calculated using M06-2X functional with 6-311++G(d,p) basis sets.

A simple univariate regression analysis considering only the electronic parameters (σv, σp, σI, *F*, and *R*) did not give satisfactory correlation. Thus we introduced molar refractivity, which is the measure of steric bulk and polarizability in our analysis.[54] A multivariate regression analysis suggested that the field and the steric effects were the two most significant variables governing the barrier.[55] A mathematical model based on these two parameters is shown as surface in Figure 7 and expressed in form of Eq.1. A negative sign of the coefficients in the equation contributed in lowering the barrier. In general, the large electron withdrawing groups lowered the barrier whereas small electron donating groups raised the barrier (Figure 7).

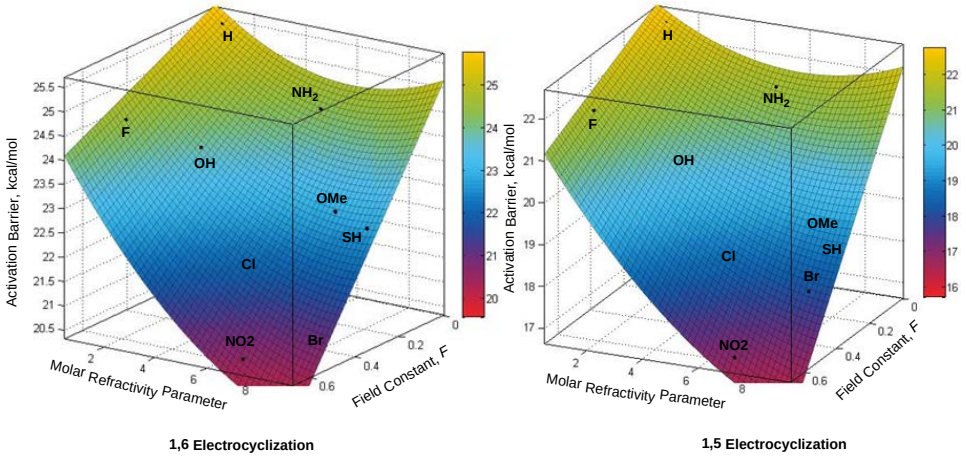

Figure 7. Dependence of activation barrier on the molar refractivity parameter and the field constant (*F*) in case of 1,6 and 1,5 electrocyclization. Linear model: z = f(x,y); z = Activation Barrier (Ea) expressed in kcal/mol, x = Field Constant and y = Molar refractivity parameter (*Mr*). For 1,6 cyclization the goodness of fit: R^2 = 0.99 Adjusted R^2 = 0.96. For 1,5 cyclization goodness of fit: R^2 = 0.9863 Adjusted-R^2 = 0.9725. The activation barriers were calculated using M06-2X functional with 6-311++G(d,p) basis sets

$$\text{Ea}\,(F, Mr) = 26.12 - 2.28F - 0.55M_r - 0.69FM_r + 0.05M_r^2 \qquad \text{(Eq. 1)}$$

$$\text{Ea}\,(F, Mr) = 22.97 - 1.94F - 0.46M_r - 0.80FM_r + 0.04M_r^2 \qquad \text{(Eq. 2)}$$

The highest barrier was observed with the unsubstituted phenyl ring. Intriguingly, three groups, CN, CHO and Me did not fit into this model.[56] Thus, we introduced other electronic parameters such as resonance (*R*), σ_p, and σ_m. As a result, -CN and –CHO substituted substrates obeyed the model with more restrictions however, methyl-substituted reactants still did not fit into this model due to steric reasons.[57] A similar surface with methyl-substituted substrate as an exception, was obtained for 1,5 cyclization (Figure 7 & Eq.2). It is worth mentioning that although the two ortho positions are simultaneously meta with respect to the other substituent, the multivariate regression analysis suggests, the effect is only minor.[58]

Position-4-Ortho Substitution. Substituents on position-2 are far enough from the reaction site to exert the steric effect. Hence, it is expected that the barriers of such substrates will only be

influenced by the electronic nature of the substituents. Furthermore, this position is simultaneously meta to the nucleophilic nitroso and para to the electrophilic alkene, thus the substituents are expected to exert multipronged electronic effects on the reaction barrier. In general, the reaction barriers with substituents on position-2 were found to be the highest among the three positions. Interestingly, the barrier for 1,5 cyclization was not only independent of the electronic nature of the substituents, but was also lower than the barrier for the substituent-dependent 1,6 pathway.[59] Analysis of variance suggested that the reaction barrier showed the best correlation with the Hammett's constants, σ_p and σ_m. The magnitude of equation coefficients shown in equation 1 suggested that the para-effect dominates over the meta effect (para: 2.84 *vs* meta: 1.41, Figure 8 and Eq. 3).

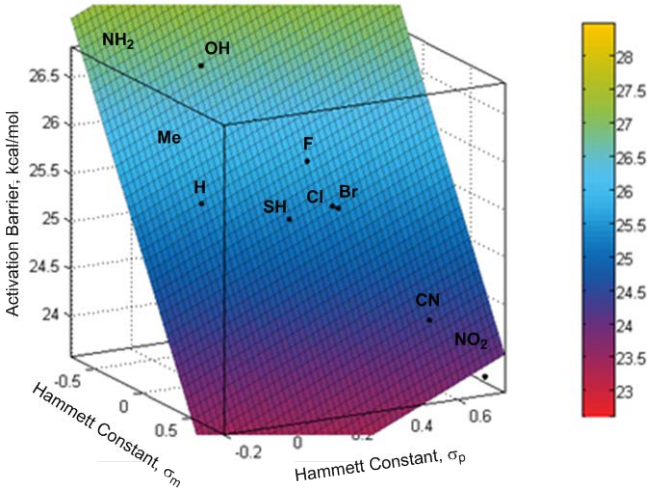

Figure 8. Correlation of 1,6 cyclization barrier with the Hammett's constants, σ_p and σ_m in the rearrangement of the position-2-substituted substrates. Goodness of fit: R^2: 0.95 Adjusted-R^2: 0.94.

$$E_a(\sigma_p,\sigma_m) = 25.33 - 2.84*\sigma_p + 1.41*\sigma_m \quad \text{(Eq. 3)}$$

Since most of the groups, except methyl and amino, that were used in this study, exert electron withdrawing meta-effect, the Hammett constants (σ_m) show a positive value.**Error! Bookmark not defined.** As a result, the positive sign of the coefficient of σ_m in Eq. 3 (+1.41) suggested that the meta-effect should contribute to raise the barrier. In contrast, the Hammett constant (σ_p) show a negative value for the electron donors and positive for the electron acceptors. Thus, the negative sign of the coefficient associated with para-effect (-2.84, Eq.3) should contribute to raise the barrier in the electron donating groups while electron-withdrawing groups should lower it. However, conformationally flexible methoxy and aldehyde groups did not obey this equation.

CONCLUSION

In summary we analyzed the mechanistic features of an unusual pseudopericyclic reaction and showed that the proximity effect is a combination of steric and electronic factors, which include chelation and hydrogen bonding. The proximity effect in case of the ortho-substituents that are close to the polar nitroso group predominantly stems from the electronic factors. In contrast to rest of the position-1 substituted substrates, an intriguing preference of 1,6 over 1,5 pathway in case of halides and methoxy have been explained by the repulsive interaction between the lone pair of electrons on the heteroatom and the developing negative charge on the nitroso group. This interaction has been shown using the molecular electrostatic potential surfaces. Furthermore, the position-1 substituted substrates, except for the outliers, obeyed correlation between the modified Swain-Lupton field constant (*F*) and the 1,6 cyclization barrier. Whereas, the same substrates followed correlation between the Hammett constant (σ_p) and the 1,5 cyclization barrier. In contrast to position-1, position-4 substituted substrates showed dependence on joint steric (*Mr*) and electronic factors (*F*). The proximity effect in this case was successfully quantified using a

multivariate regression analysis. Furthermore, we observed that the methyl group generally does not fit in the trend when placed at position-1 or 4 primarily due to steric reasons. Finally, position-2, which is expected to influence the reaction barrier electronically, had negligible on 1, 5 cyclization whereas 1, 6 cyclization was jointly governed by σ_p, σ_m, *F*, and *R*. Thus, the present modeling of proximity effect sheds light on the interplay of forces that the control the chemical reactivity of ortho-substituted aromatic systems. Understanding of these forces can further aid in the synthesis of multi-substituted aromatic systems.

COMPUTATIONAL METHODS

All geometries were optimized using Gaussian 03 program (see reference) at the M06-2X/6-311g++(d,p) level which performs well for the compounds containing main group elements. The optimized equilibrium structures were found to be true minima with no imaginary frequency whereas transition state (TS) geometries had only one imaginary frequency (see SI).

ASSOCIATED CONTENTS

Supporting Information. Geometries, energies, frequencies of all transition states, reactants and products. Multivariate regression analysis. Table containing barriers for all substrates. "This material is available free of charge via the Internet at http://pubs.acs.org."

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Notes

On 9th November 2014, Professor Marie E. Krafft, Co-author of this manuscript has passed away.

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(53) Unlike hydroxyl, the amino-substituted substrate is stabilized to a far lesser extent than the transition state. As a result the activation barrier is not affected. This is corroborated by the natural charges, H-bond distances, second order perturbation analysis and the IR stretching frequencies (See SI for the detailed figure depicting the comparison of hydroxyl and amino groups).

(54) Molar refractivity is calculated by Hansch and Leo equation: MR = $4/3\pi NA\alpha$. Hansch, C., Leo, A., **1995**. Exploring QSAR – Fundamentally and application in chemistry and biology. *Amer. Chem. Soc*., Washington, DC. C. Hansch, A. Leo, D. Hochman, **1995**. Exploring QSAR – Hydrophobic, Electronic and Steric Constant. *Amer. Chem. Soc*., Washington, DC.

(55) Molar refractivity is expressed in terms of m3/mol. Thus we decided to normalize molar refractivity of the all groups with respect to hydrogen. As a result, the energy equation obtained from the bivariate analysis contains units of energy. Bivariate linear regression analysis suggested that the barrier was function of field constant and the square of molar refractivity parameter.

(56) When CN is included in the model, the Ea (F,M_r) = 25.74 - 1.92F - 0.30M_r - 0.58FM_r + 0.02M_r^2. Goodness of fit: R^2 = 0.94, Adjusted-R^2 = 0.89.

(57) Ea = 20.78 – 0.31M_r + 66.9 σ_p – 225.8 σ_m + 169.4F. Goodness of fit: R^2 = 0.95, Adjusted-R^2 = 0.91.

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(59) Barrier for 1,5 cyclization was calculated ~22 kcal/mol for most of the substrates. See SI for the precise values.

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