Tetrahedron Letters 58 (2017) 3362–3365

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Predicting the regioselectivity of nucleophilic addition to arynes using frontier molecular orbital contribution analysis

Saber Mirzaei [a,*], Hormoz Khosravi [b]

[a] Faculty of Chemistry, Razi University, P.O. Box: 67149-67346, Kermanshah, Iran
[b] Faculty of Chemistry, K. N. Toosi University of Technology, P.O. Box: 15418-49611, Tehran, Iran

ARTICLE INFO

*Article history:*
Received 20 May 2017
Revised 28 June 2017
Accepted 12 July 2017
Available online 14 July 2017

*Keywords:*
Aryne
Contribution analysis
Frontier molecular orbital
Regioselectivity

ABSTRACT

The regioselectivity of nucleophilic addition to substituted arynes was predicted using frontier molecular orbital contribution analysis. This model indicates that the percentage of the LUMO on the reacting terminus of the aryne is responsible for the observed regioselectivity; the nucleophile attacks the carbon possessing higher contribution of the LUMO.



Understanding the chemistry of arynes (benzynes, indolynes, pyridynes) is an intriguing subject in organic chemistry.[1] In recent years the regioselectivity of nucleophilic addition to arynes has been one of the most challenging facets of understanding these highly reactive triple bonds for both synthetic and computational chemists. Several groups have tried to justify the regioselectivity of nucleophilic addition to arynes based on the charge distribution, steric effects and electron density.[2,3] Finally, Houk and co-workers proposed a model based on distortion effects.[4] In this model the distortion of arynes is responsible for their regioselectivity; the flatter the internal angle, the more favorable the terminus for nucleophilic attack. According to this model, the flatter terminus is more electrophilic and also requires less distortion energy in its transition state structure for reaction with a nucleophile. Angle differences of ~4° or greater represent synthetically useful levels of regioselectivity, while lower values correspond to low and variable levels of selectivity.

Additionally, Houk and co-workers employed frontier molecular orbital (FMO) coefficients to qualitatively justify the regioselectivity of cycloaddition reactions.[5] However, using the FMO coefficients was not useful in justifying the selectivity and reactivity of some cycloaddition reactions (e.g. cycloaddition of Münchnone derivatives).[6] To the best of our knowledge, the applicability of FMO theory for predicting the regioselectivity of nucleophilic addition to arynes has not been previously examined. Therefore, despite the success of the distortion model, herein, we report a model based on FMO theory. In this study, contribution analysis (CA) was used instead of the orbital coefficients. This model can predict the regioselectivity of nucleophilic attack on arynes based on the contribution that the reacting terminus has on the frontier orbital, the lowest unoccupied molecular orbital (LUMO), for arynes as an electophile.[7] It should be noted that neither the distortion nor frontier molecular orbital contribution analysis (FMO-CA) approaches take into account the steric factors.

Garg and Houk reported a systematic study of the regioselectivity for the nucleophilic addition to 3-substituted benzynes (Fig. 1). They justified their selectivity based on the distortion model.[8] In order to evaluate the applicability of the FMO-CA model, these 3-substituted benzynes were selected as the first group of arynes to be examined.

In general, there are two different approaches toward performing contribution analysis; i) methods based on the wave function (e.g. Mulliken, Stout-Politzer, SCPA) and ii) methods based on the electron density (e.g. Hirshfeld, Becke). In order to find the best method and evaluate their basis set dependency, the LUMO-CA of the five 3-substituted benzynes were calculated using three different basis sets (ESI, Tables S1–S5). Table 1 lists the standard deviation (SD) of these calculations. The Hirshfeld method showed the lowest SD (0.1), therefore, this method was used for all calculations. Also, the standard deviation of the Becke method was very low (0.2) which indicates the superiority of density based methods over the wave function based methods for these examples.[9]

* Corresponding author.
*E-mail address:* sabermirzaei@live.com (S. Mirzaei).

http://dx.doi.org/10.1016/j.tetlet.2017.07.047
0040-4039/

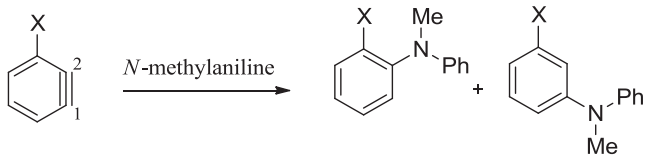


**Fig. 1.** Nucleophilic addition of *N*-methylaniline to the model 3-substituted benzynes.

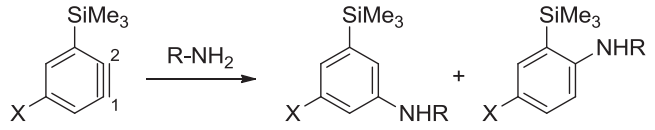


**Fig. 2.** Nucleophilic addition of amines (R-$NH_2$) to model 3-(trimethylsilyl) benzynes.

**Table 1**
Standard deviation (SD) of five contribution analysis methods using three different basis sets (6-31G*, 6-311++G(2d,2p), aug-cc-pVTZ) for the model 3-substituted benzynes (Fig. 1). All values obtained using the B3LYP functional.

| X | Mulliken | Stout-Politzer | SCPA | Hirshfeld | Becke |
|---|---|---|---|---|---|
| OMe | 3.2 | 2.6 | 4.0 | 0.2 | 0.1 |
| F | 0.6 | 4.8 | 5.1 | 0.0 | 0.2 |
| Cl | 1.9 | 6.0 | 5.3 | 0.0 | 0.2 |
| Br | 1.3 | 12.8 | 4.4 | 0.1 | 0.3 |
| I | 2.3 | 42.4 | 4.7 | 0.2 | 0.1 |
| Average SD | 1.9 | 13.7 | 4.7 | 0.1 | 0.2 |

**Table 2**
LUMO-CA (B3LYP/6-31G*) of the model 3-substituted benzynes and their experimental ratios.

| Entry | X | C1% | C2% | Δ(C1-C2)% | Experimental ratio (C1:C2)[8] |
|---|---|---|---|---|---|
| 1 | OMe | 41.3 | 32.3 | 9.0 | >99 |
| 2 | F | 42.1 | 34.0 | 8.1 | >99 |
| 3 | Cl | 40.8 | 35.5 | 5.3 | 20:1 |
| 4 | Br | 40.6 | 35.8 | 4.8 | 13:1 |
| 5 | I | 40.3 | 35.9 | 4.4 | 9:1 |

Table 2 lists the LUMO-CA for the model 3-substituted benzynes using the Hirshfeld method. The values were obtained from the fully optimized structures (B3LYP/6-31G* and LanL2DZ for iodine).[9] As illustrated in Table 2, 3-methoxy benzyne (X = OMe) showed the highest difference between the C1 and C2 termini (C1-C2 = 9.0%) with the nucleophile preferentially attacking at the carbon with higher LUMO contribution (C1). The regioselectivity of 3-methoxy benzyne has been reported by several groups,[10] each reporting C1 as the favored site of nucleophilic attack. This regioselectivity prediction was also valid for all remaining 3-substituted benzynes (Table 2).[8]

The experimental ratios (Table 2) indicated almost identical selectivity for the methoxy and fluorine groups (Entries 1 and 2).[8] However, FMO-CA and distortion models show different selectivity for OMe and F. Based on the distortion model, the F substituted benzyne has a larger internal angle difference (17°) in comparison to OMe (15°). In contrast, the LUMO-CA indicates OMe (C1-C2 = 9.0%) as more selective in comparison to F (C1-C2 = 8.1%). Also, the $\Delta\Delta G^{\ddagger}$ ($\Delta G^{\ddagger}(C1) - \Delta G^{\ddagger}(C2)$) values show higher selectivity for OMe (5.2 kcal/mol) in comparison to F (4.1 kcal/mol).[8] In this example the FMO-CA model is in better agreement with the obtained transition states energy differences ($\Delta\Delta G^{\ddagger}$).

The experimental ratios (Table 2) shows decreasing selectivity from F to I; the LUMO-CA predicts the same trend. The F and I substituents showed the highest (C1-C2 = 8.1%) and the lowest (C1-C2 = 4.4%) difference in favor of C1, respectively. Regarding the halogen containing benzynes (Entries 2–5), it appears that their selectivity depends on the electronegativity of the substituted atom; the greater electronegativity of the halogen leads to a higher degree of regioselectivity. The calculated LUMO-CA values, compared to the experimental observations, reveal the quantitative application of the FMO-CA model. These results are independent of the selected DFT functional (ESI, Table S6 and S7).

**Table 3**
LUMO-CA (B3LYP/6-31G*) of the model 3-(trimethylsilyl) benzynes and their experimental ratios.

| Entry | X | R | C2% | C1% | Δ(C2-C1)% | Experimental ratio (C2:C1)[11] |
|---|---|---|---|---|---|---|
| 1 | Me | Furfuryl | 39.2 | 35.0 | 4.2 | 5.6:1 |
| 2 | Ph | Cyclohexyl | 38.9 | 34.6 | 4.3 | 5.9:1 |
| 3 | OMe | Allyl | 39.8 | 34.6 | 5.2 | 6.0:1 |
| 4 | F | $CH_2Ph$ | 40.1 | 34.4 | 5.7 | 8.5:1 |
| 5 | Cl | NHBoc | 39.9 | 33.4 | 6.5 | 16.0:1 |

The regioselectivity of substituted 3-(trimethylsilyl) benzynes (Me, Ph, OMe, F, Cl) was also investigated (Fig. 2). In all cases C2 possessed higher LUMO-CA values. Therefore, this terminus is the preferred site of attack, which was in agreement with the experimental outcomes (Table 3). This selectivity was attributed to the strong inductive effects of the silyl substituent.[11] According to the experimental ratio, the C2 selectivity was not significantly affected by the substituents. However, the selectivity of Entry 5 is higher which can be attributed to the greater nucleophilicity of the *tert*-butyl carbamate (NHBoc). In spite of the insignificant substituent effects, the calculated LUMO-CA values were in good agreement with the experimental ratios. The distortion model indicates identical angle differences for Me, Ph and OMe (~12°) and also for F and Cl (~14°).

In order to examine the generality of the FMO-CA model, several arynes for which their experimental regioselectivities has been determined were investigated (Table 4). Also, the FMO-CA model was tested for several arynes which do not have reported experimental observations (ESI, Table S8). The first five entries examine different indolyne structures. The LUMO-CA indicates a higher value on C5 (38.6%) of 4,5-indolyne in comparison to C4 (37.4%, Entry 1). This regioselectivity is overturned in 6-bromo-4,5-indolyne (Entry 3). Additionally, Br substitution at C3 enhances the selectivity of 4,5-indolyne, increasing the C4 preference from 1.2% to ~3% (Entry 2). This selectivity enhancement was also reported experimentally.[12] The FMO-CA model correctly predicts the selectivity for both 5,6- and 6,7-indolynes (Entries 4 and 5).[12] The obtained values for Entries 1–5 show FMO-CA as a useful model for the quantitative determination of regioselectivity.

The C3 position of 3,4-pyridyne (Entry 6) shows a higher value (37.4%) in comparison to C4 (36.5%). However, the experimental data showed either no or very weak C4 selectivity in the nucleophilic addition reaction.[13] Based on the distortion model, the internal angle of C4 is bigger than C3, which eventuates in greater electrophilicity at C4. It should be noted that C3 shows a lower transition state (~0.4 kcal/mol) in the nucleophilic addition reaction.[13b] This lower barrier can be attributed to the better interaction of 3,4-pyridyne and the nucleophile frontier orbitals. Nevertheless, it seems that the distortion model has better agreement with the experimental observations for 3,4-pyridyne. The addition of different substituents to 3,4-pyridyne can alter its regioselectivity (Entries 7 and 8), and the FMO-CA model correctly predicts these substitution effects. In contrast to