

Generation, structure and reactivity of arynes: A theoretical study

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Abstract. The semiempirical AM1 SCF-MO method is used to study the benzyne mechanism for aromatic nucleophilic substitution of various *m*-substituted chlorobenzenes and 3-chloropyridine. The calculations predict that most of the fixed substituents studied here would induce the formation of 2,3-arynes through their electron-withdrawing resonance or inductive effects. The geometry and electronic structure of the 2,3- and 3,4-arynes investigated here, confirm the generally accepted *o*-benzyne structure postulated for arynes. The sites of nucleophilic addition to arynes as predicted here are in fair agreement with expectation and experimental findings.

Keywords. Benzyne mechanism; aryne bond; nucleophilic addition to arynes; AM1 SCF-MO method.

1. Introduction

Arynes are reactive intermediates derived from substituted arenes which participate in some aromatic nucleophilic substitutions^{1–3} and some cycloaddition reactions⁴. They are a neutral ring species which in the case of benzyne may be represented by resonance structures **1** and **2** contributing to the hybrid **3** (figure 1), of which structure **1** contributes more⁵. The formal triple bond of structure **1** calls for *sp* hybrid carbons at the two bond termini. The rest of the ring skeleton consists of *sp*² carbons, so that the aromatic sextet is still retained in the aryne⁶. Arynes are so highly reactive that they exist as stable species only at very low temperatures, e.g. 8 K for benzyne⁵. Arynes may be derived from substituted benzenes, fused arenes and pyridines⁷.

1.1 The benzyne mechanism

This consists of 1,2-elimination of the haloarene followed by nucleophilic addition. The 1,2-elimination step involves deprotonation by a strong base with departure of the halide anion⁶ yielding the aryne intermediate. The nucleophile then adds on to the triple aryne bond yielding a substituted arene.

1.2 Direction of aryne bond formation

For substrates like aryl halides and *o*- or *p*-disubstituted cases having a fixed substituent *Z*, only one proton can be abstracted and only one aryne formed⁸. For the *m*-disubstituted

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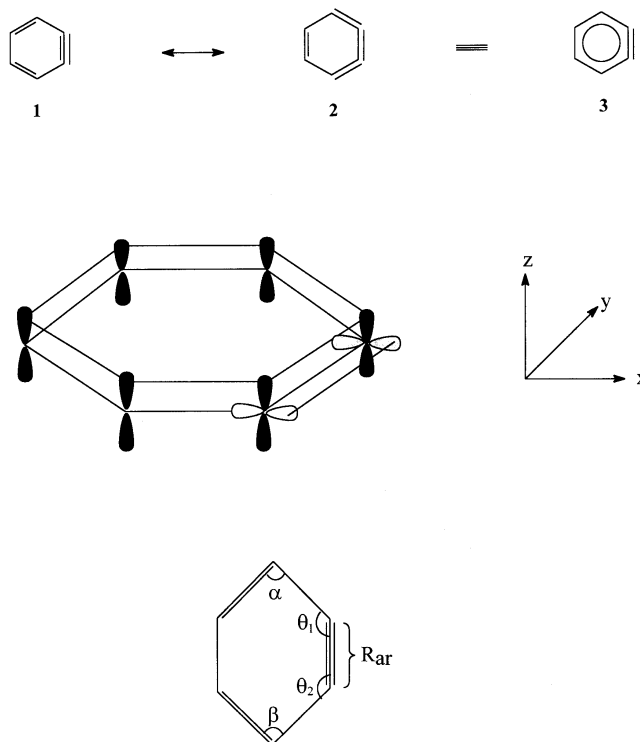


Figure 1. Resonance structures and aromatic sextet of benzyne, with geometry determinants R_{ar} , α , β , θ_1 and θ_2 .

case, which of the two hydrogens is abstracted depends upon their relative acidities. This in turn depends upon the effect of the fixed group Z ¹.

The effect of the Z group upon proton acidity is shown in figure 2. In case 2a, Z is an electron-withdrawing group through resonance, where the canonical structure **5** is more stable due to less charge separation. The *o*-hydrogen is more acidic due to the positive charge on the *o*-carbon of **5**, leading to a 2,3-aryne. In case 2b, the electron-withdrawing inductive effect of Z induces greater positive charge on the *o*-hydrogen again, so that a 2,3-aryne is formed. In case 2c, Z donates electrons via resonance, where the structure **8** is more stable than **9** due to less charge separation. The negative charge on the *o*-carbon of **8** directs the base to the *p*-hydrogen, leading to a 3,4-aryne. In case 2d for the pyridine **10**, the negative charge on the ring nitrogen with its lone pair directs the base to the *p*-hydrogen, resulting in a 3,4-aryne. 3,4-Arynes may in general, be obtained from *p*-substituted halobenzenes, while 2,3-arynes always result from the *o*-substituted cases.

1.3 Structural aspects of aryne

Three structures have been postulated for aryne – the monocyclic *o*-benzyne, the bicyclic *m*-benzyne and the bicyclic *p*-benzyne structures. Restricted Hartree–Fock *ab initio*

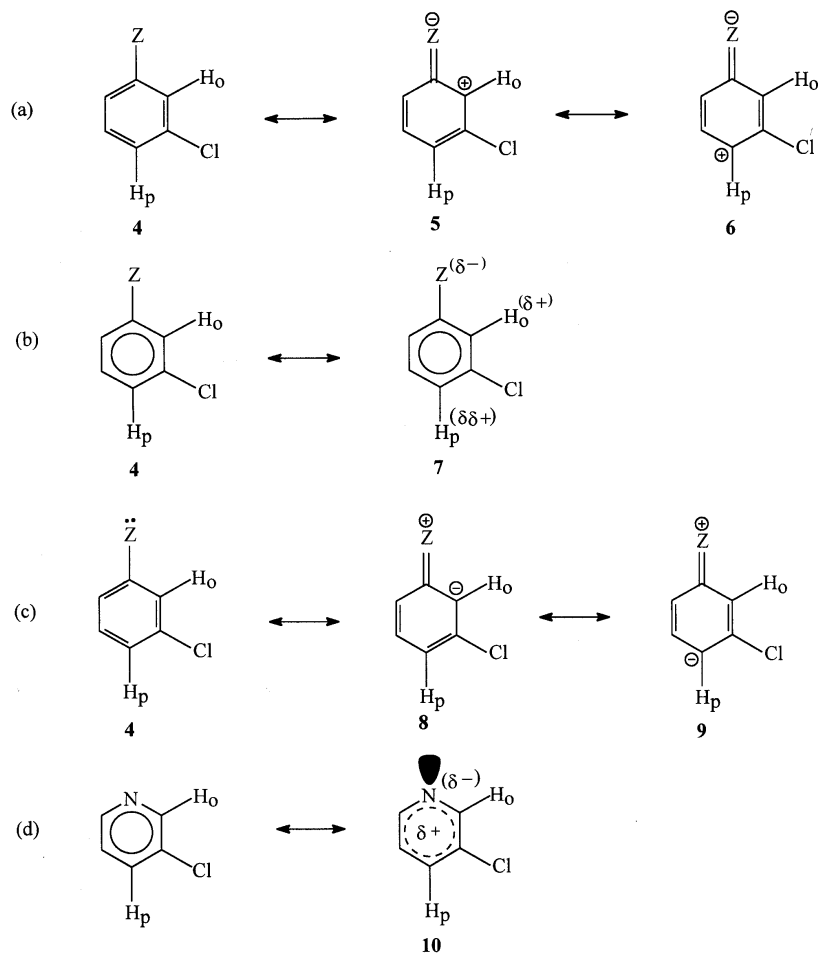


Figure 2. Modes of influence of fixed substituent Z upon acidities o - and p -hydrogens.

studies have indicated a ground singlet state in the stability order: ortho < meta < para⁹. A MINDO/3 study predicted singlet ground states for all the three isomeric benzyne¹⁰. An *ab initio* study on *o*-benzyne indicated a triple bond only 0.03 Å longer than that of acetylene¹¹. A similar study on *m*-benzyne predicted a bicyclic structure, less stable by 11 kcal/mol than *o*-benzyne¹². The three isomeric benzyne have been studied¹³ using a 4-31 G extended basis set, and predict the energy ordering ortho < meta < para. The generalised Hartree-Fock method has been used to predict the same ordering¹⁴. The consensus of opinion is that the ortho structure is the most likely one, and this structure alone has been adopted for this study.

The unique feature of aryne geometry (figure 1) concerns itself with the aryne bond length R_{ar} , the angles θ_1 and θ_2 between the aryne bond and the adjacent C-C bonds, and

ϕ_d the dihedral angle encompassing the aryne bond. To these may be added the angles α and β between the C–C bonds adjacent to the aryne bond and the C–C bond immediately attached to them but away from the aryne bond. The Wiberg bond order W_{ar} for the aryne bond is also noted.

1.4 Site of nucleophilic addition

The site preferred for nucleophilic addition to the aryne bond depends again on the fixed substituent Z ¹⁵. For 2,3-arynes, figure 3 depicts four ways in which Z could operate. Case 3a applies to electron-withdrawing Z groups acting through resonance. Here the canonical form **12** is the stablest structure, and directs nucleophilic attack to the positively charged *o*-carbon, leading to an *o*-product. In case 3b, Z withdraws electrons by the inductive effect, and results in an *o*-product again. In case 3c, Z donates electrons by resonance,

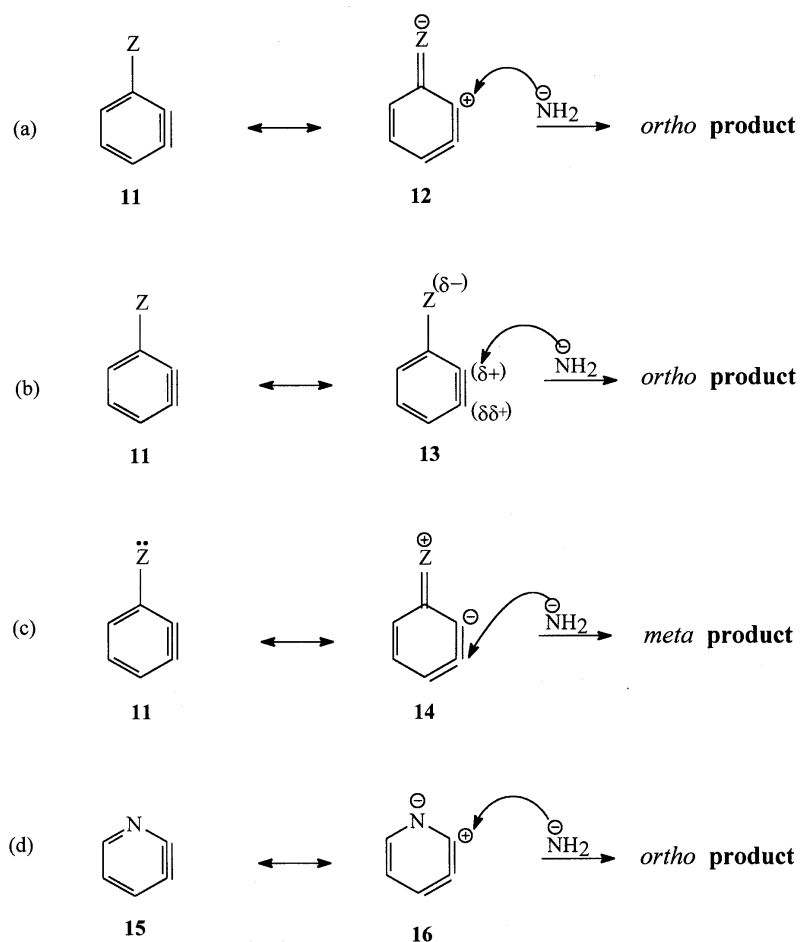


Figure 3. Modes of influence of fixed substituent Z upon direction of nucleophilic attack of NH_2^- upon 2,3-arynes.

with structure **14** as the most stable resonance structure. The negative charge on the *o*-carbon leads to the meta product. For the 2,3-pyridyne case, structure **16** is stable, with positive charge on the *o*-carbon; an *o*-substituted product would be expected.

The possibilities open for 3,4-arynes are depicted in figure 4. In case 4a, the electron-withdrawing mesomeric effect of *Z* makes the *p*-carbon more positive than the *m*-carbon, leading to *p*-attack of the nucleophile. Case 4b shows how the inductive effect of *Z* creates more positive charge on the *m*- than on the *p*-carbon, leading to a *m*-substituted product. For case 4c, the electron-donating resonance effect of *Z* makes the *p*-carbon more negative than the *m*-one thereby leading to preferential attack of the nucleophile at the *m*-position. In the 3,4-pyridyne case of 4d, the *p*-carbon is activated towards nucleophilic attack, resulting in a *p*-substituted product.

1.5 Scope of this study

This semiempirical SCF-MO study probes the characteristic features of the benzyne mechanism in disubstituted cases where one substituent *Z* is fixed, and the other a

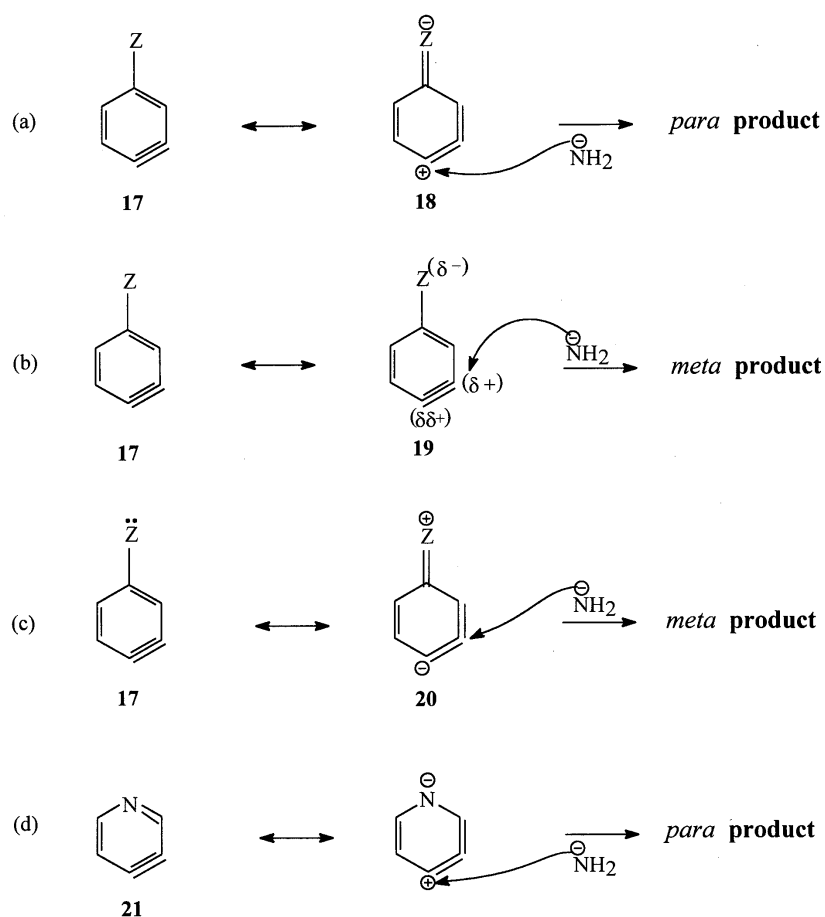


Figure 4. Modes of influence of fixed substituent *Z* upon direction of nucleophilic attack of amide anion on 3,4-arynes.

m-chloro substituent. Various *m*-substituted chlorobenzenes are chosen for study here, with the fixed substituent *Z* being Cl, F, CH₃, NH₂, NO₂, CN, OH, OCH₃, and the *m*-chloropyridine case. This is done to predict the direction of aryne bond formation for *m*-chlorobenzenes. Both the 2,3- and the 3,4-arynes (having the same fixed 1-substituents *Z*) are studied with regard to their structural aspects and also with regard to the direction of nucleophilic addition. The base used for study here is the amide anion, which also functions as the nucleophile being added.

2. Theoretical methodology

The semiempirical AM1 SCF-MO method¹⁶ of the MOPAC package was used to provide the wave-function for the parent *m*-chlorobenzenes, the 2,3- and the 3,4-arynes. Complete unconstrained geometry optimisation was performed through the Davidon–Fletcher–Powell routine. Starting geometries for stable precursors were built up from standard molecular data. Those for the aryne species were constructed by simple removal of the two atoms H and X which leave during 1,2-elimination.

2.1 Indices for direction of aryne bond formation

AM1 indices were framed to compare the acidities of *o*- and *p*-hydrogens of various *m*-substituted chlorobenzenes (enumerated earlier) to predict the direction of aryne bond formation. The *o*-hydrogen is labelled as *O*, and the *p*-hydrogen as *P*. These indices include:

(i) The net Mulliken charge Q_h on the hydrogen abstracted; (ii) the Wiberg bond index W_{ch} for the strength of the C–H bond broken during proton abstraction; (iii) the enthalpy ΔH_a of the net aryne formation reaction given as



Preferential abstraction of the *o*-proton leads to 2,3-aryne formation, while that of the *p*-proton leads to a 3,4-aryne.

2.2 Indices for direction of nucleophilic addition

The aryne bond carbon atom nearer to the fixed substituent *Z* is termed as A, while that further away is termed as B. The indices of relevance for nucleophilic addition include Q_a and Q_b , the Mulliken charges on A and B respectively, as well as the frontier orbital indices T_a and T_b for atoms A and B respectively, where

$$T_a = C_x^2 + C_y^2, \quad (2)$$

where C_x and C_y are the $2px$ and $2py$ atomic orbital coefficients of the carbon atom in the lowest empty molecular orbital (LEMO) involving this atom (A or B). The charge indices Q_a and Q_b represent the hard–hard Coulombic interactions between proton and base, while T_a and T_b represent soft–soft covalent interactions involving orbital overlap.

3. Results and discussion

The 8 *m*-substituted chlorobenzenes mentioned earlier along with 3-chloropyridine were considered to predict the direction of aryne bond formation. Both 2,3- and 3,4-arynes

were chosen to predict the direction of nucleophilic addition, having the same substituents *Z* as those chosen to study aryne bond formation.

3.1 Direction of aryne bond formation

Table 1 gives the AM1 indices for acidity of the *o*- and *p*-protons involved, viz. the electron density indices Q_h and W_{ch} as well as the enthalpy index ΔH_α . These indices are labelled as *O*- and *P*- for the *o*- and *p*-protons respectively. The favoured aryne product (whether 2, 3 or 3, 4 or either) is mentioned in the table 1 as well as the relevant *Z* effect operating (see figure 2).

For the cases where *Z* is Cl, F, NO₂, CN, OH, and OCH₃, these indices on the whole, furnish the same predictions that the *o*-proton would be more acidic, favouring the 2,3-aryne product. The $\Delta H_\alpha(o)$ and $\Delta H_\alpha(p)$ values for the Cl, CH₃, NH₂, NO₂, CN, OH, and OCH₃ cases here exhibit small percentage differences. This leads us to resort chiefly to the charge and bond strength indices as determinants for proton acidity. These inferences point to the mesomeric electron-withdrawing effects of the NO₂ and CN groups. Apparently, the AM1 method treats the Cl, F, OH and OCH₃ groups as electron-withdrawing through their inductive effects.

For the CH₃ and NH₂ cases, all the three indices are marked by similar *o*- and *p*-values, predicting that both 2,3- and 3,4-arynes could be generated. The situation here is corroborated by the experimental results on 1,2-elimination of *m*-dihalobenzenes^{15,17}. Here, the CH₃ case behaves almost like the unsubstituted case, with both 2,3- and 3,4-arynes being formed. The NH₂ case also predicts little difference between the 2,3- and the 3,4- aryne. For the pyridine case, the results clearly predict formation of the 3,4-aryne.

3.2 Structural features of arynes

Table 2 presents the value ranges for the determinants of geometry around the aryne bond for 2,3- and 3,4-arynes. It is seen that the aryne bond is shorter than the usual value of about 1.4 Å for a delocalised C–C bond in arenes, being about 1.25 to 1.27 Å in length.

Table 1. AM1 data* for facility of aryne generation from *m*-chlorosubstituted benzenes and 3-chloropyridine using electron distribution indices (Q_h and W_{ch}) and the enthalpy ΔH_α for dehydrohalogenation reaction by amide anion. O and P stand for the ortho and para cases respectively.

<i>Z</i>	$Q_h(O)$	$Q_h(P)$	$W_{ch}(O)$	$W_{ch}(P)$	$\Delta H_\alpha(O)$	$\Delta H_\alpha(P)$	Major aryne	Factor
Cl	0.1607	0.1499	0.9418	0.9451	28.59	28.92	2, 3	2b
F	0.1627	0.1508	0.9418	0.9450	51.11	66.61	2, 3	2b
CH ₃	0.1466	0.1461	0.9455	0.9459	27.65	28.60	2, 3 & 3, 4	
NH ₂	0.1463	0.1470	0.9449	0.9457	25.94	28.94	2, 3 & 3, 4	
NO ₂	0.1845	0.1584	0.9331	0.9428	30.44	30.33	2, 3	2a
CN	0.1598	0.1524	0.9424	0.9444	28.83	28.65	2, 3	2a
OH	0.1647	0.1483	0.9406	0.9456	29.81	29.20	2, 3	2b
OCH ₃	0.1620	0.1464	0.9415	0.9462	29.39	29.18	2, 3	2b
⁺ -N=	0.1522	0.1737	0.9440	0.9280	39.03	30.11	3, 4	2d

*The Q_h and W_{ch} indices in atomic units; ΔH_α in kcal/mol; ⁺For 3-chloropyridine

Table 2. Ranges of values* for determinants of geometry in arynes including bond length R_{ar} , bond angles θ_1 , θ_2 , α and β , dihedral angle ϕ_d , and Wiberg bond index W_{ar} .

Index	Range	
	2, 3-Arynes	3,4-Arynes
R_{ar}	1.2540–1.2689	1.2572–1.2671
θ_1	126.30–135.44	126.62–128.55
θ_2	123.22–129.69	125.84–129.13
α	104.84–110.27	107.82–112.49
β	108.46–109.15	108.28–109.01
ϕ_d	– 0.58–+ 0.02	– 0.66– + 0.09
W_{ar}	2.2872–2.3891	2.3048–2.3684

* R_{ar} in angstroms; θ_1 , θ_2 , α , β , and ϕ_d in degrees; W_{ar} in atomic units.

The θ_1 and θ_2 angles deviate somewhat from the usual sp^2 angle of about 120° , and display values ranging mostly from 123.2° to 135.4° . The α and β angles show marked deviation from the usual sp^2 value, ranging from about 105 to 112° . This could indicate a role on the part of the adjacent C–C bonds to compensate for the ring distortion caused by the aryne triple bond.

That the aryne is basically planar may be gauged from the values of the dihedral ϕ_d which is always close to zero. This planarity speaks of the aromatic character of the aryne species, where the aromatic sextet is retained despite the formal triple bond of the molecule. The high value of W_{ar} is as expected for the aryne multiple bond, ranging from 2.29 to 2.39 atomic units, as compared to about 1.67 au for the usual aromatic C–C bond.

3.3 Site of nucleophilic addition

Table 3 presents AM1 data for comparing reactivity of the two carbons of the aryne bond towards nucleophilic addition of ammonia (as amide anion). Both 2,3- and 3,4-arynes are considered. The direction of nucleophilic addition is predicted chiefly by the charge indices Q_a and Q_b , which are significant here owing to the “hard” character of the NH_2^- nucleophile. In fact, the “soft” T_a and T_b indices do not furnish predictions in line with those from the “hard” indices, and are not relied on to explain the “hard–hard” interactions expected here.

For the 2,3-arynes, preferential attack at the *m*-position is predicted when the fixed substituent *Z* is F, Cl, NH_2 , OCH_3 , OH and CH_3 . This corroborates their role as electron-donating substituents. The F, Cl, NH_2 , OCH_3 and OH groups here act after the fashion of figure 3c, viz. through their lone-pair resonance effects. The methyl case presumably acts in the same manner through hyperconjugation. For the electron-withdrawing NO_2 and CN substituents as well as the 2,3-pyridine case, attack is predicted to occur at the *o*-position, which is in accord with the *Z* effect given in figures 3a and d. These predictions for 2,3-arynes are quite in accord with the expected trend.

For the 3,4-arynes, the electron-withdrawing effect of the NO_2 and CN groups is predicted to lead to a para product, as shown in figure 4a. The 3,4-pyridyne case is also predicted to result in a *p*-substituted product after the manner of figure 4d. Substitution at the *m*-position is predicted to occur for the F, Cl, NH_2 , OCH_3 , OH and CH_3 cases, in line with their electron-donating resonance effect depicted in figure 4c.

Table 3. AM1 data for addition of nucleophile NH_2^- to 2,3-arynes and 3,4-arynes including the hard charge indices Q_a and Q_b , and the soft overlap indices T_a and T_b (all indices in atomic units).

Z	Q_a	Q_b	T_a	T_b	Site	Effect
<i>2,3-Arynes</i>						
Cl	-0.1198	-0.0991	0.5445	0.5600	meta	3c
F	-0.1634	-0.0777	0.5338	0.5639	meta	3c
NH_2	-0.2086	-0.0684	0.5375	0.5598	meta	3c
NO_2	-0.0477	-0.1065	0.5431	0.5611	ortho	3a
OCH_3	-0.1461	-0.0829	0.5429	0.5527	meta	3c
CN	-0.0843	-0.1144	0.5421	0.5564	ortho	3a
OH	-0.1466	-0.0774	0.5423	0.5545	meta	3c
Me	-0.1260	-0.0340	0.5547	0.5515	meta	3c
$-\text{N}^*=\text{}$	-0.0475	-0.1738	0.5429	0.5527	ortho	3d
<i>3,4-Arynes</i>						
Cl	-0.1192	-0.1130	0.5322	0.5590	para	4c
F	-0.1055	-0.1234	0.5437	0.5685	meta	4c
NH_2	-0.0970	-0.1542	0.5404	0.5681	meta	4c
NO_2	-0.1258	-0.0271	0.5320	0.5546	para	4a
OCH_3	-0.1012	-0.1441	0.5372	0.5663	meta	4c
CN	-0.1244	-0.0946	0.5445	0.5621	para	4a
OH	-0.0973	-0.1450	0.5411	0.5662	meta	4c
Me	-0.1230	-0.1260	0.5481	0.5614	meta	4c
$-\text{N}^*=\text{}$	-0.1675	-0.0936	0.5543	0.5432	para	4d

*Denotes the case of pyridine

3.4 Correlations with experimental results

Reference is made here to some early results on the product distribution of the attack of substituted chlorobenzenes by NaNH_2 /liquid ammonia via the benzyne mechanism.

3.4a Treatment of chlorotoluenes: Among *o*-, *m*- and *p*-chlorotoluenes⁸ the ortho case leads to 45% *o*-amino product and 55% *m*-amino product, as shown in figure 5a. The meta case of figure 5b leads to 40% *o*-amino, 52% *m*-amino and 8% *p*-amino products. The para case of figure 5c yields 62% *m*-amino and 38% *p*-amino products. These results may be rationalised by referring to our theoretical data of tables 1 and 3 as follows.

The ortho case can generate only the 2,3-aryne because of the absence of another hydrogen ortho to the 2-chloro substituent. This 2,3-aryne (1-methyl-2,3-aryne) is predicted by the data of table 3 to yield the *m*-amino product as the major one. This is found experimentally to be the case, albeit by a rather small margin, which is in line with the electron-donating properties of the methyl substituent.

The meta case presents an ambiguity in aryne generation. The data of table 1 predicts that both the 2,3- and the 3,4-arynes would be formed in comparable amounts. From the 2,3-aryne, the *m*-amino product is predicted by table 3 to be the major one, and the *o*-amino product minor. From the 3,4-aryne, table 3 again predicts the *m*-amino product to be the major one, leading eventually to the conclusion that the *m*-amino product would be the major one overall from *m*-chlorotoluene, as is indeed so experimentally.

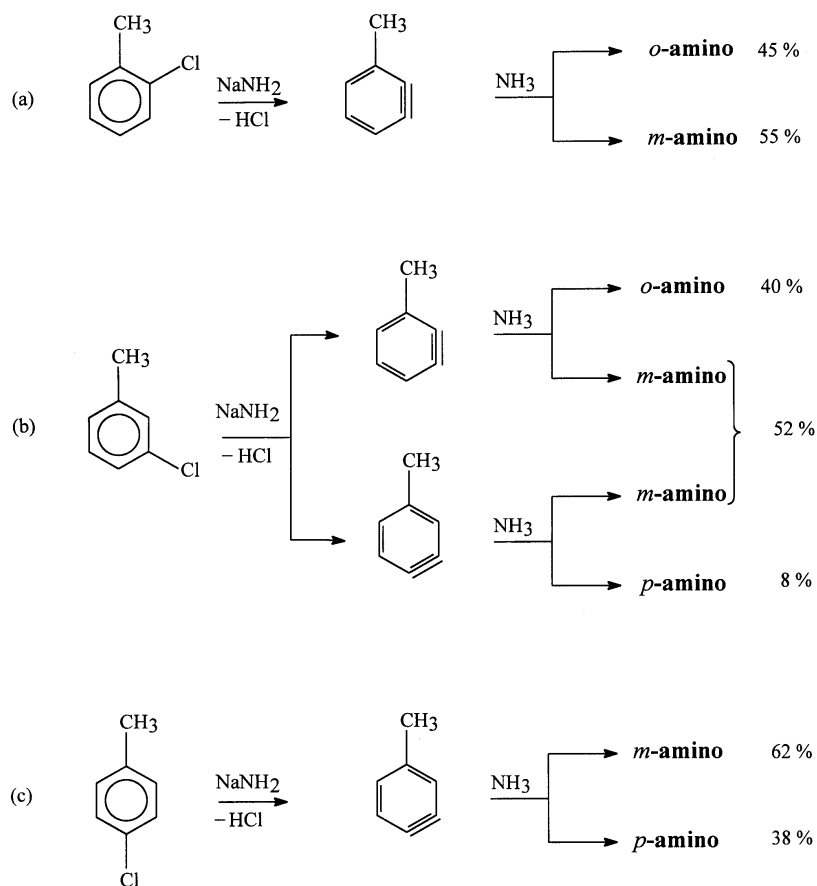


Figure 5. Aryne generation and amino product formation for *o*- and *p*-chlorotoluenes⁸.

For the case of *p*-chlorotoluene, only the 3,4-aryne is generated, for which table 3 predicts that the *meta* amino product would be the major one, as found experimentally.

3.4b *Treatment of dichlorobenzenes:* The early work of Wotiz and Huba¹⁵ indicated that *o*-dichlorobenzene yields the *m*-amino product as major, the *m*-isomer giving the *m*-amino product as major, while the para case leads to the *p*-amino major product. These may be rationalised as follows (figure 6).

The ortho case has no ambiguity, yielding only the 2,3-aryne. This species is predicted by table 3 to yield the *m*-amino product as major, which indeed, is the case.

The *meta* case could yield both the 2,3- and the 3,4-arynes, for which table 1 predicts that the 2,3-aryne intermediate would predominate. This 2,3-aryne is predicted by table 3 to give the *m*-amino product as major, while the corresponding 3,4-aryne gives the *p*-amino product as major. If we assume the 2,3-aryne is formed in large excess over the 3,4-aryne, then the major product predicted for the 2,3-aryne would indeed be the overall major product. This assumption apparently holds, as may be inferred from the data of Wotiz and Huba.

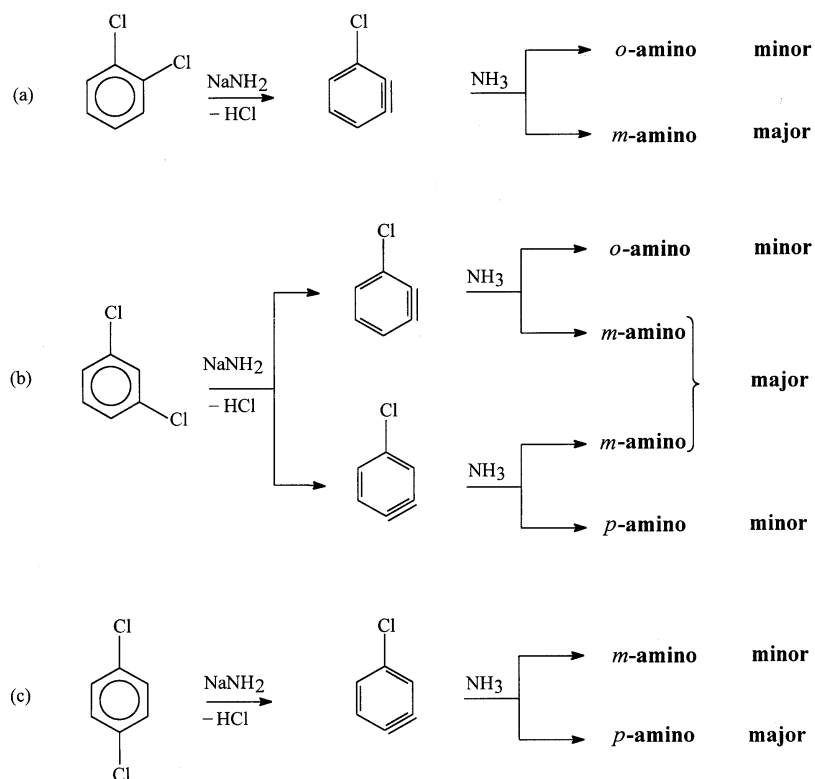


Figure 6. Aryne generation and amino product formation of *o*-, *m*- and *p*-dichlorobenzenes¹⁵.

For the para case, the 3,4-aryne generated is predicted by table 3 to yield the *p*-amino product as major, which is supported by the findings of Wotiz and Huba.

4. Summary and conclusions

This theoretical study leads to the following inferences:

(i) For the benzyne reaction involving *m*-substituted chlorobenzenes, the presence of F, Cl, NH₂, OH and OCH₃ groups as fixed substituents leads to preferential formation of 2,3-arynes through their inductive effects. This inference is subject to question for the NH₂, OH and OCH₃ cases, but follows expectation for the F and Cl cases. The NO₂ and CN groups are correctly predicted to yield the 2,3-arynes, while the 3-chloropyridine is predicted to yield a 3,4-aryne.

(ii) Results are more congruent for predicting the effect of fixed substituent Z upon addition of ammonia to 2,3-arynes. The *m*-product is predicted for the F, Cl, NH₂, OCH₃, OH and CH₃ cases for 2,3-arynes, as fits their role as mesomeric electron-donating groups. Prediction of the *o*-products for the NO₂, CN and pyridyne cases of 2,3-arynes is in line with their electron-withdrawing effects.

- (iii) Similarly, for the 3,4-arynes, the *m*-product is predicted for the F, NH₂, OCH₃, OH and CH₃ cases, as expected from their electron-donating effects. The *p*-product is predicted for the electron-withdrawing cases of NO₂, CN and the pyridyne case.
- (iv) The geometry and structure of 2,3- and 3,4-arynes as predicted here, is much in line with what is generally accepted. These include the multiple aryne bond, aromatic planarity and compensation by other C–C bonds to accommodate the aryne bond.
- (v) For chlorotoluenes and dichlorobenzenes, predictions are made regarding the product distribution of the benzyne reaction. These are quite in consonance with the observed findings.

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