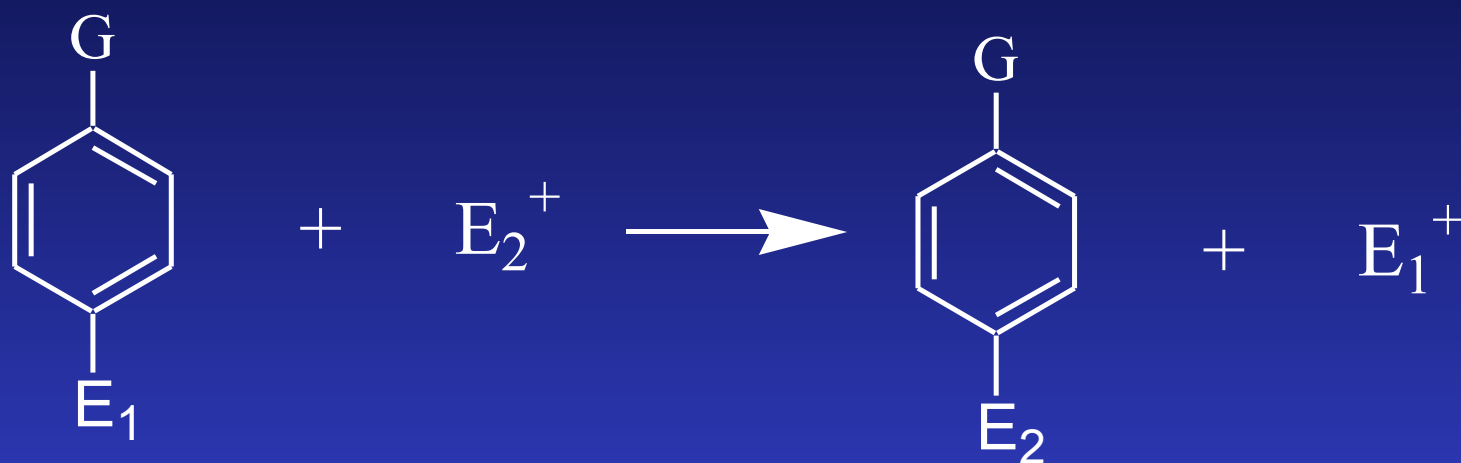


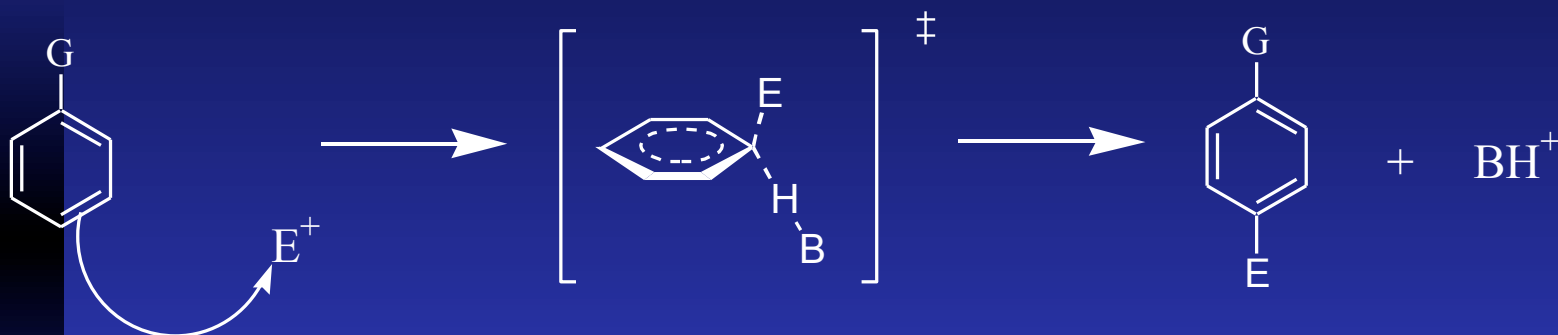
Electrophilic Aromatic Substitution – S_E2



Mechanisms of Reaction

■ Ingold-Hughes (original idea)

- ◆ Advantage: aromaticity is maintained in the direct displacement

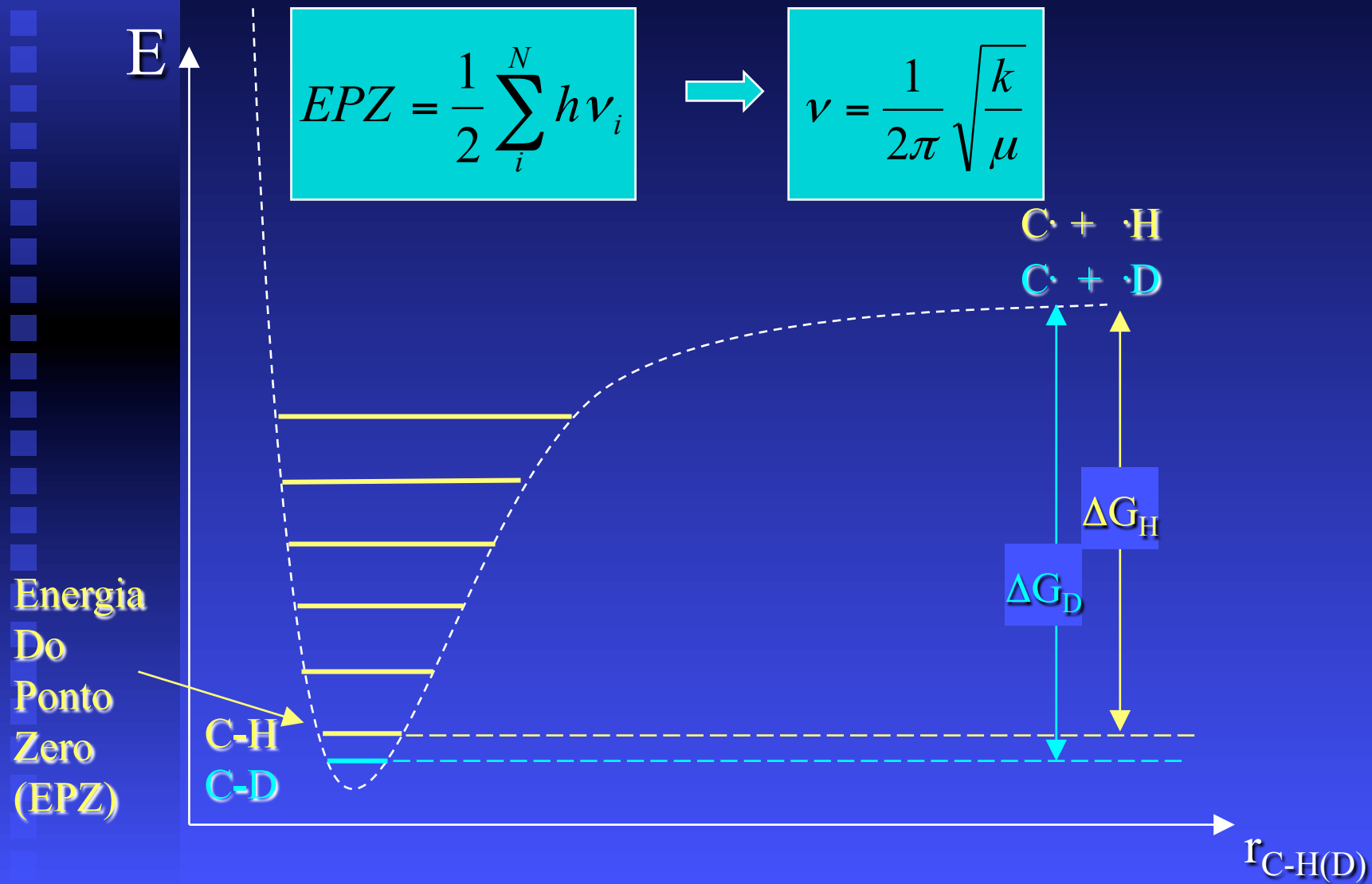


■ Melander

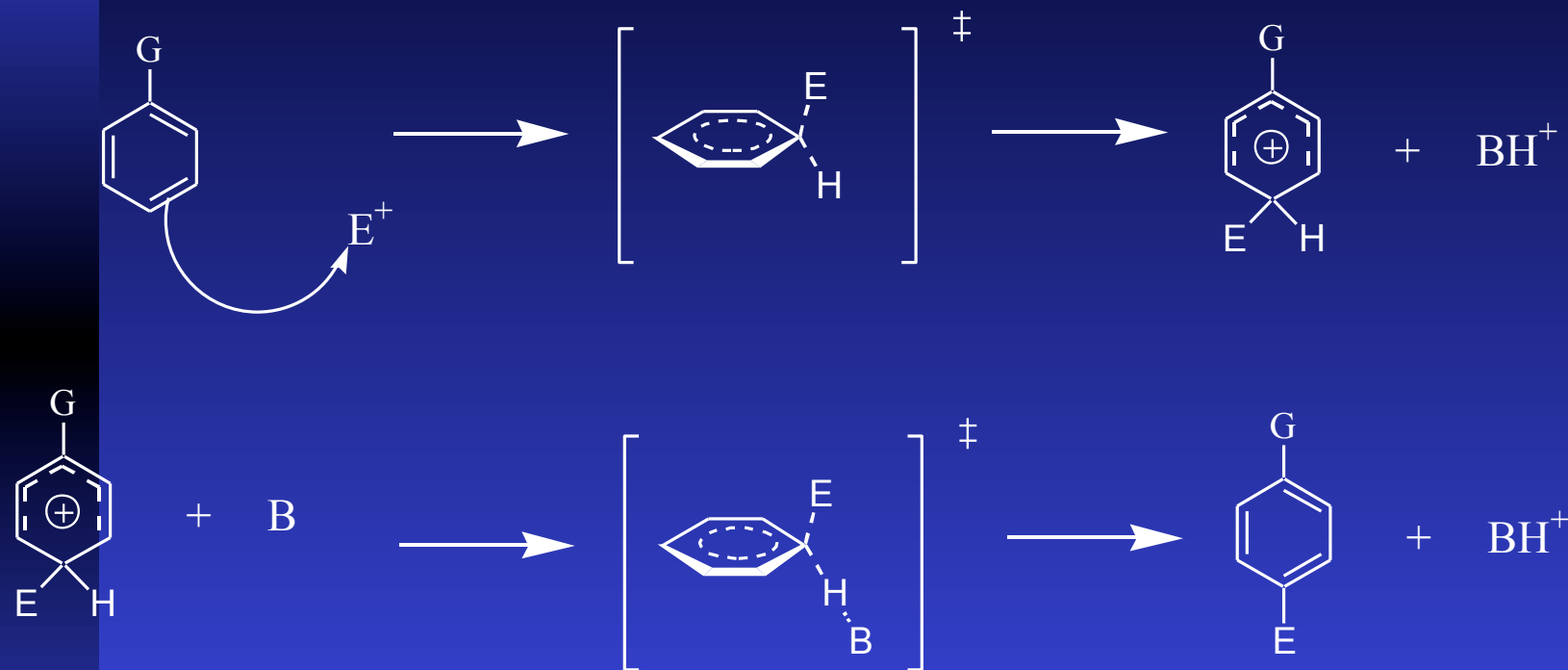
- ◆ Secondary kinetic isotopic effect for nitration and bromination of aromatics

Reaction	k_H/k_D
Benzene + HNO ₃ /H ₂ SO ₄	0.89
Toluene + NO ₂ ⁺ BF ₄ ⁻	0.85

Efeito Cinético Isotópico



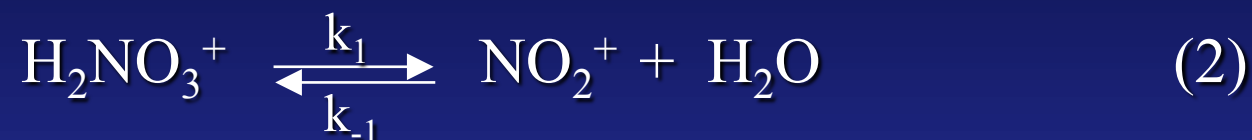
Modified Ingold-Hughes Mechanism



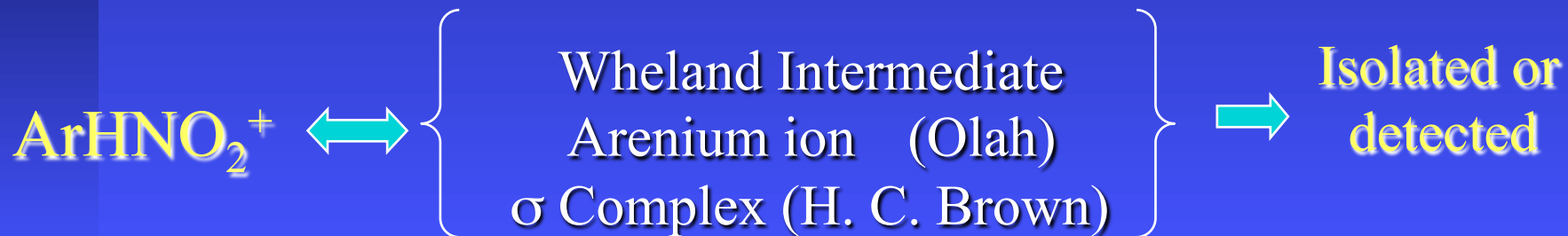
σ -Complex : strong bonding between reactants

“Accepted” Mechanism for Nitration

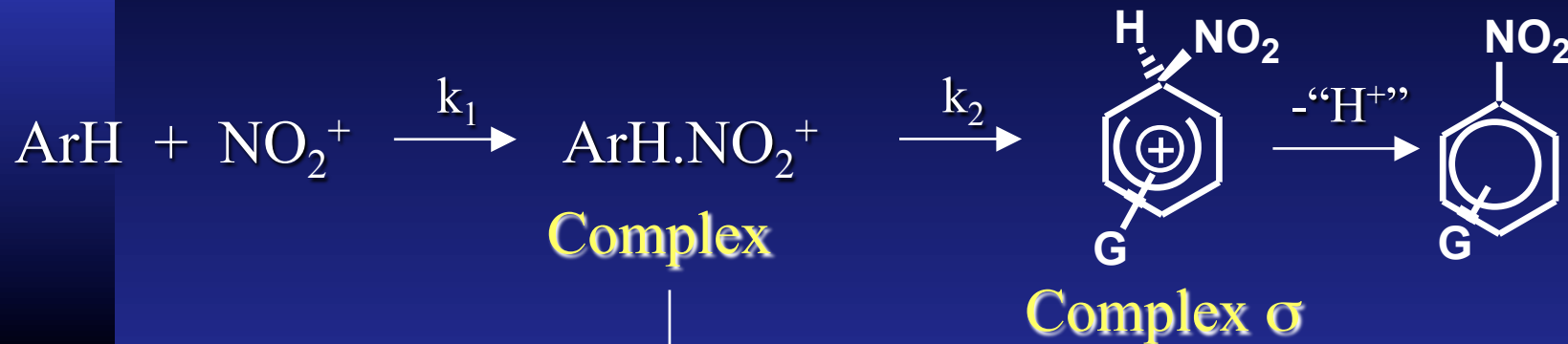
•Ingold-Hughes (Polar) Mechanism



 **Reaction Intermediate**



Modified Mechanisms



π Complex

- Interaction between reactants
- π system is involved with the NO₂⁺ as a whole

(Olah)

Encounter Pair

- No interaction between the reactants
- Random collision of species leads to the σ complex
- Reactants are trapped into the solvent cage

(Schofield)

SET

- Charge Transfer complex
- Formation of ArH⁺ and NO₂
 - Depends on ionization potential of the aromatic

(Kerner, Weiss, Perrin, Ebersson, Kochi)

SET Mechanism

- **Kenner (1945) and Weiss (1946)**
 - Single Electron Transfer from ArH to NO_2^+
- **Perrin (1977)**
 - Nitronaphthalene from naphthalene under NO_2 and electrolysis
 - Same product ratio for α and β (10:1) nitronaphthalene as that found in $\text{HNO}_3/\text{H}_3\text{CCN}$



Oxidation potentials of aromatics more activated than toluene are lower than oxidation potentials of NO_2



SET is exothermic

Perrin, C. L.; *J. Am. Chem. Soc.* 1977, 99, 5516

SET Mechanism

- **Kochi, 1981**

- Nitration with NO_2Y ($\text{Y} = \text{OH}, \text{OAc}, \text{NO}_3, \text{Cl}, \text{Py}, \text{C}(\text{NO}_2)_3$)
- $\text{NO}_2\text{Y} + \text{aromatics} \rightarrow$ **Observation of absorption bands in the UV/Vis spectrum**

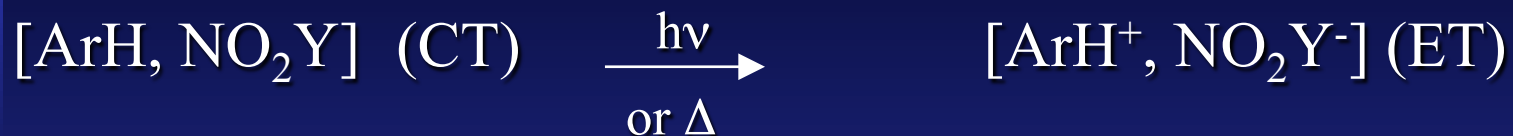


Typical for Charge Transfer complexes



Intramolecular

Perrin and Kochi's Mechanism



Rate controlling: Single Electron Transfer (SET)

Spin density: Controls Regioselectivity

Problems: small k predicted for an outer sphere complex (Marcus Theory)
Explain low ipso substitution despite the high spin density on this position

Ion-Molecule Reactions in the Gas Phase

- **Olah, Dunbar:** ICR (Ion Cyclotron Resonance)



- **Cacace and col., ICR**



Gas phase results disfavor the mechanism of Schofield, since there is complex formation and there is no solvent involved

Controversy: Nature of the intermediate observed before the σ complex $\left\{ \begin{array}{l} \text{Single electron transfer ?} \\ \pi \text{ Complex} \end{array} \right.$

Mechanistics Aspects

Initial approach: *ab initio/DFT* calculations

J|A|C|S
A R T I C L E S

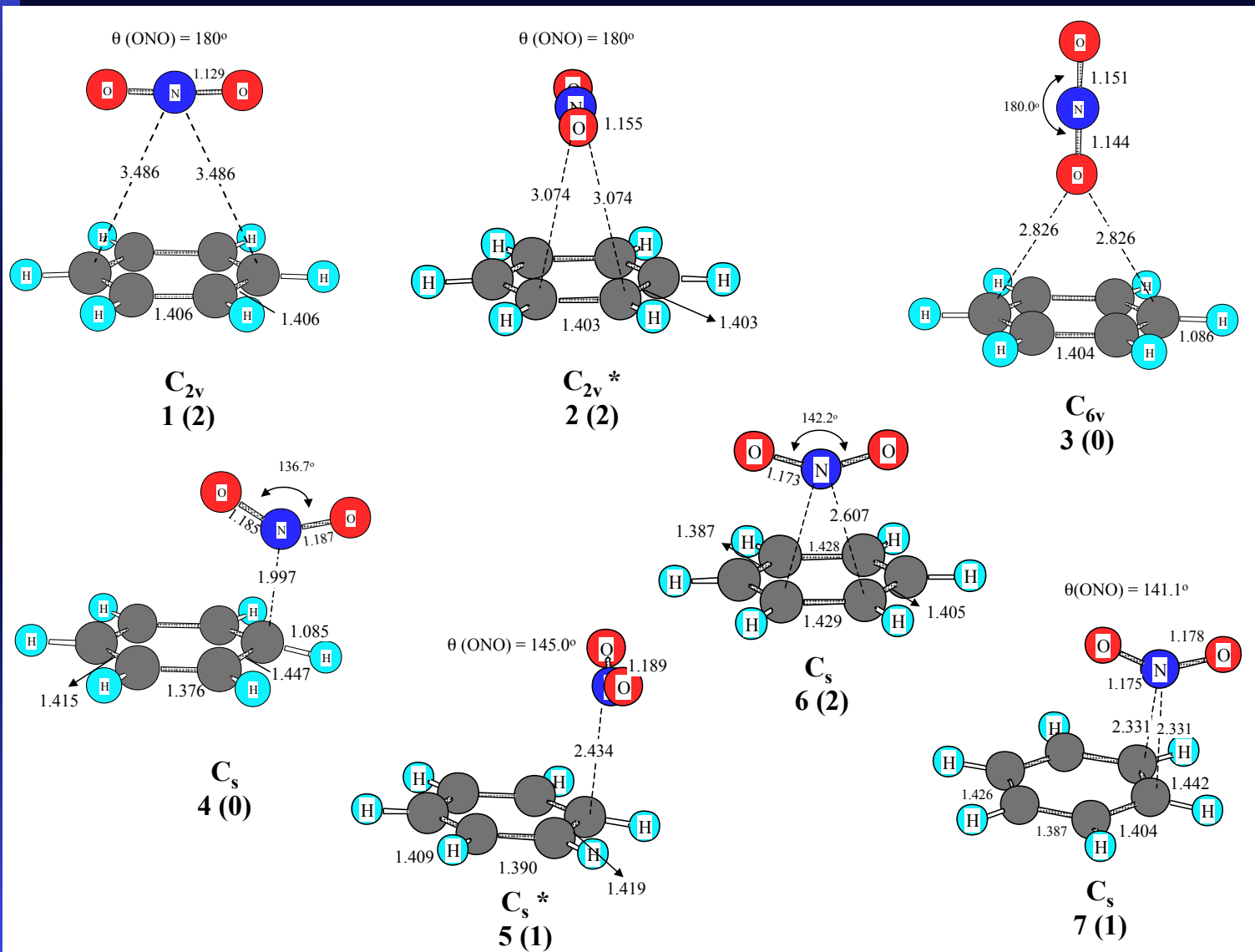
Published on Web 03/28/2003

Unified Mechanistic Concept of Electrophilic Aromatic Nitration: Convergence of Computational Results and Experimental Data

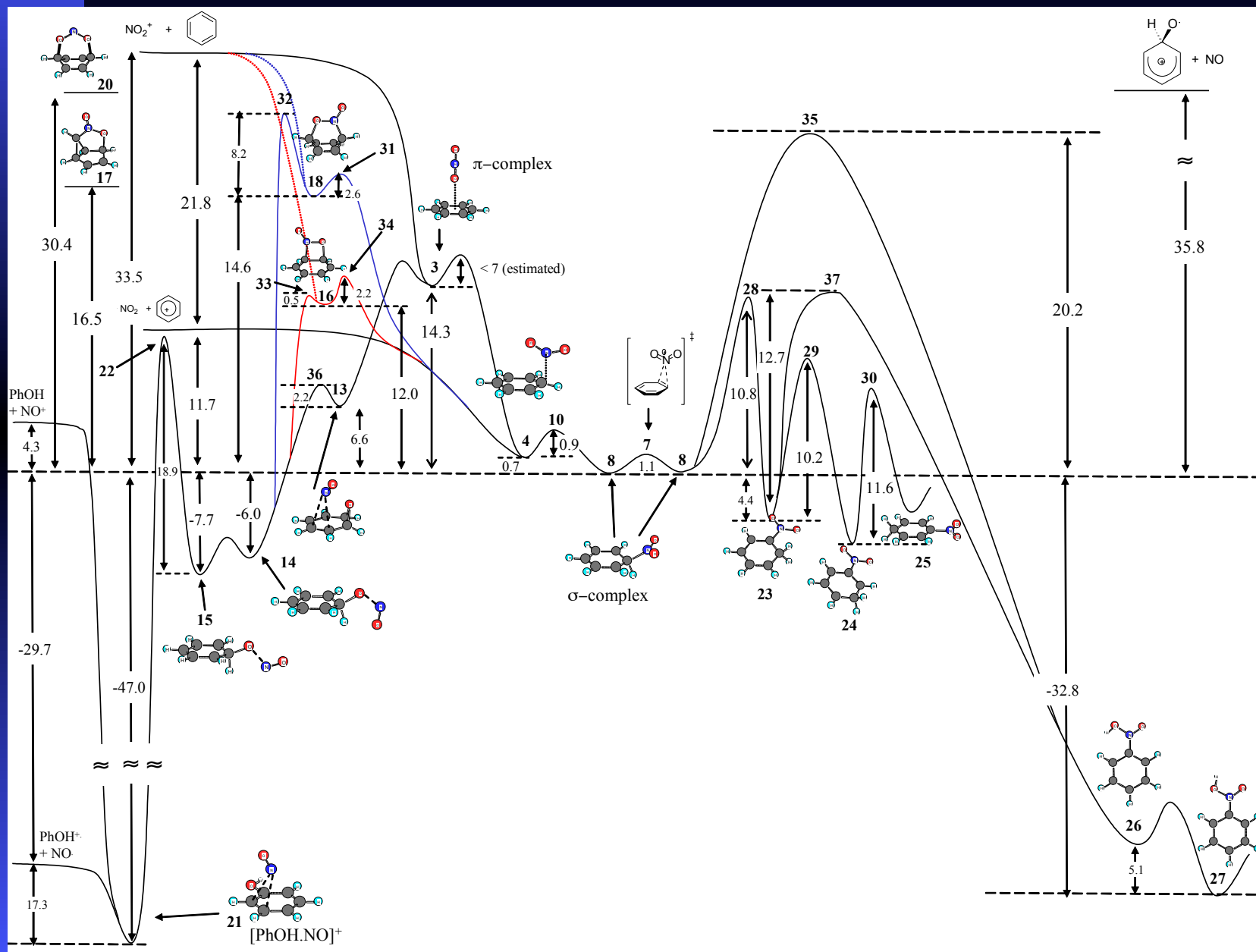
Pierre M. Esteves,^{*,†,‡,⊥} José Walkimar de M. Carneiro,[§] Sheila P. Cardoso,[§]
André G. H. Barbosa,[‡] Kenneth K. Laali,^{||} Golam Rasul,[†] G. K. Surya Prakash,[†] and
George A. Olah^{*,†}

J. AM. CHEM. SOC. 2003, 125, 4836–4849

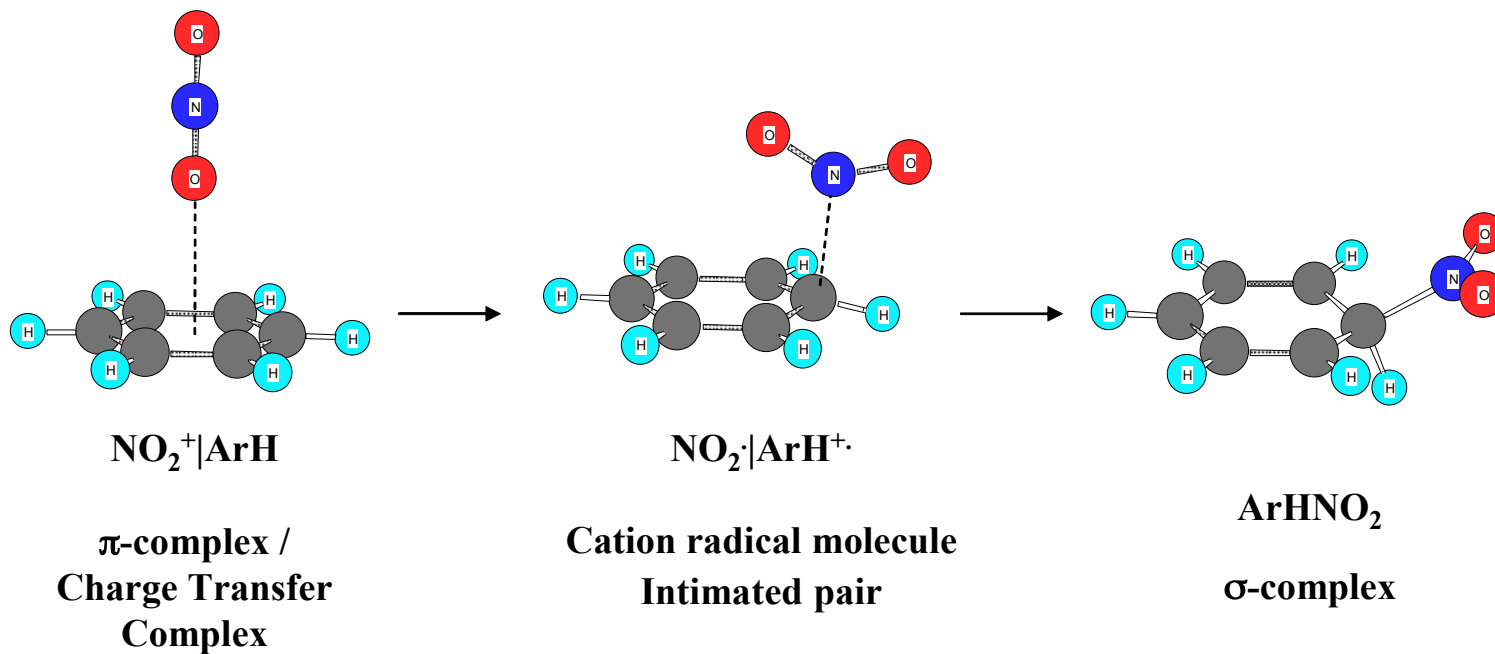
Initial Approach: π Complexes?



B3LYP/6-311++G**//B3LYP/6-31++G** calculations



Key intermediates



Unoriented complex \rightarrow Electrostatic nature (π)

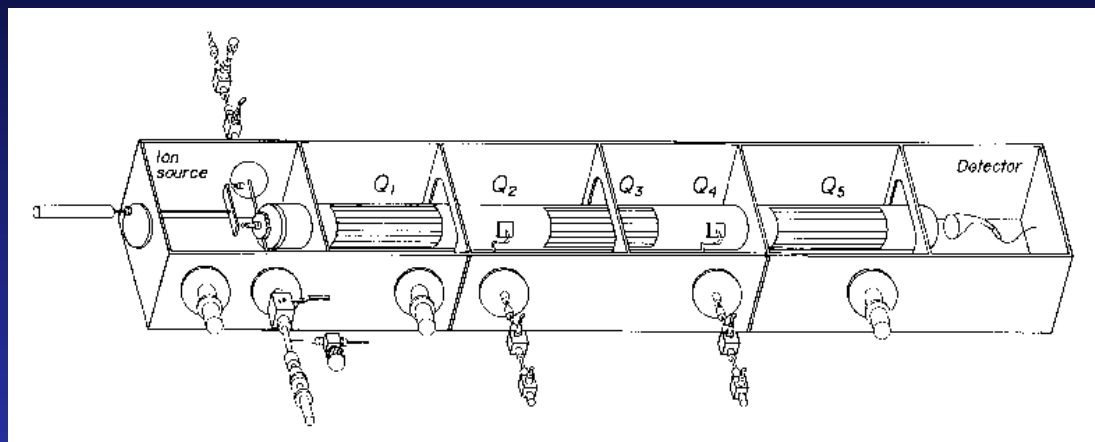
Oriented complex \rightarrow SET intimate pair



Avoided crossing between different electronic states

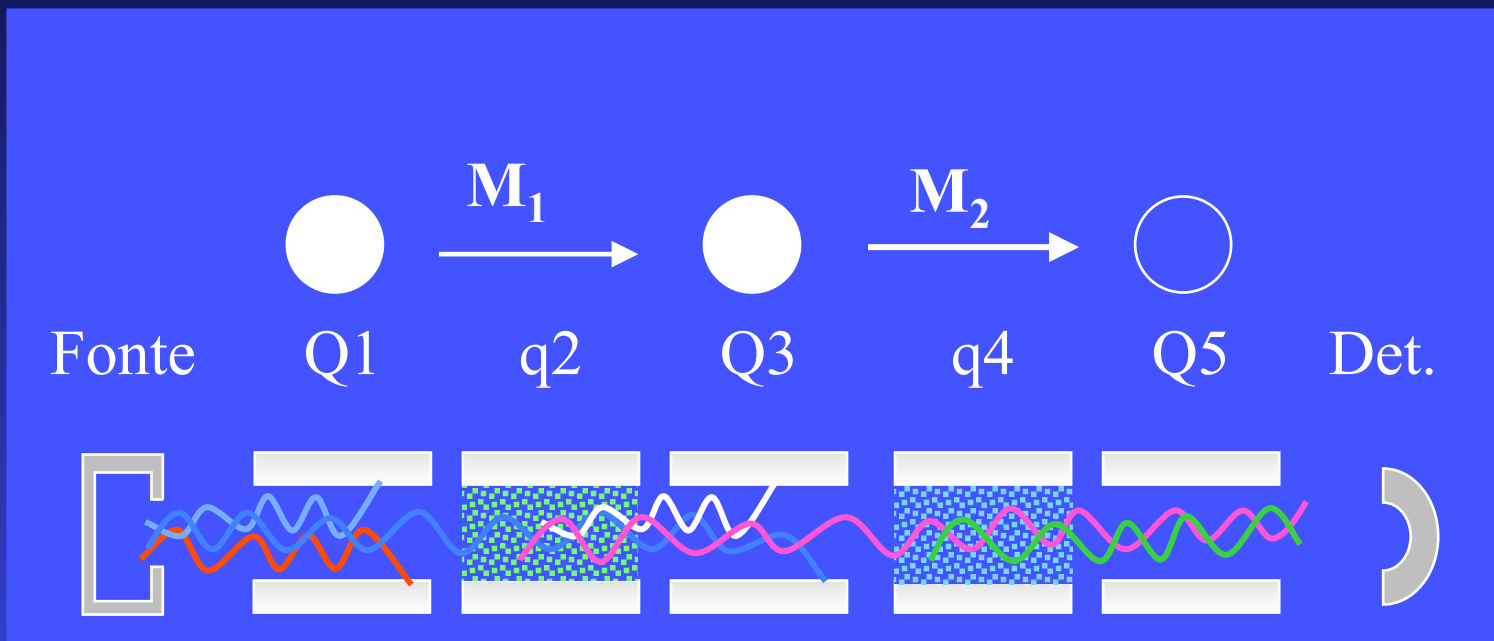
Ion-Molecule Reaction in the Gas Phase: Pentaquadrupole MS
Colaboration with Prof. Marcos N. Eberlin (State University of Campinas – Brazil)

• *Extrel Pentaquadrupole QqQqQ Mass Spectrometer (MS³)*



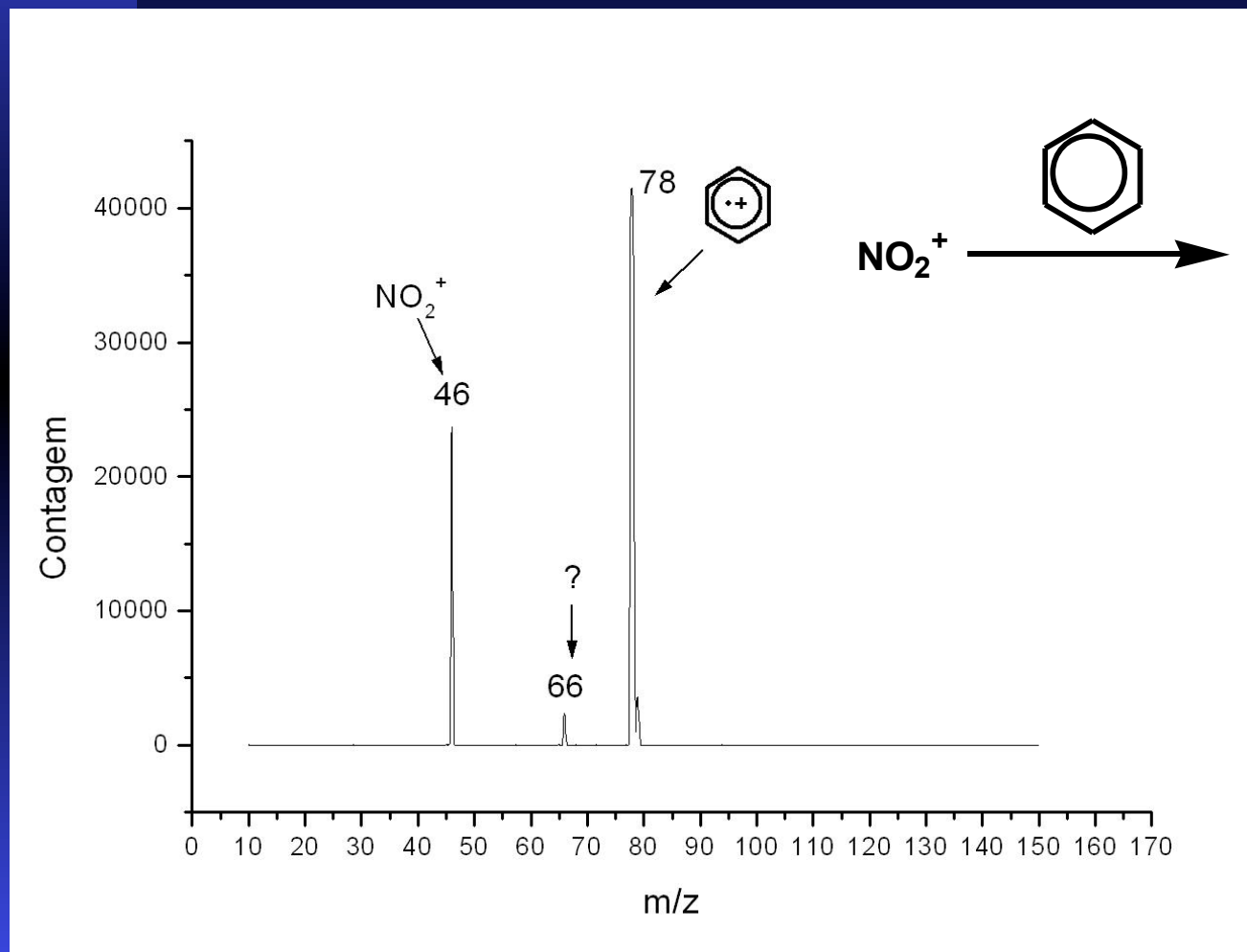
Eberlin, M. N. *Mass Spectrom. Reviews* 1997, 16, 113

• *Extrel Pentaquadrupole QqQqQ Mass Spectrometer (MS³)*



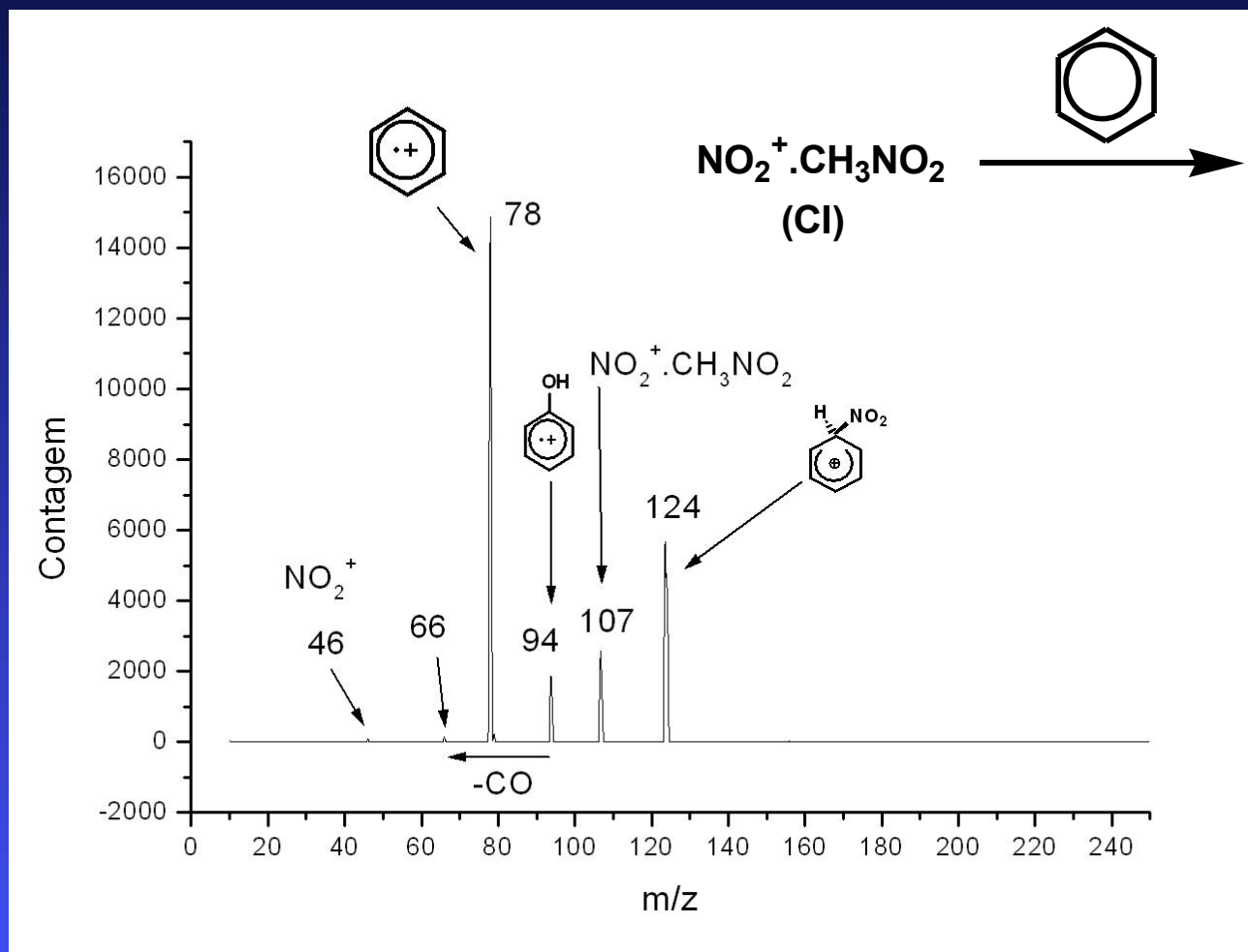
Eberlin, M. N. *Mass Spectrom. Reviews* 1997, 16, 113

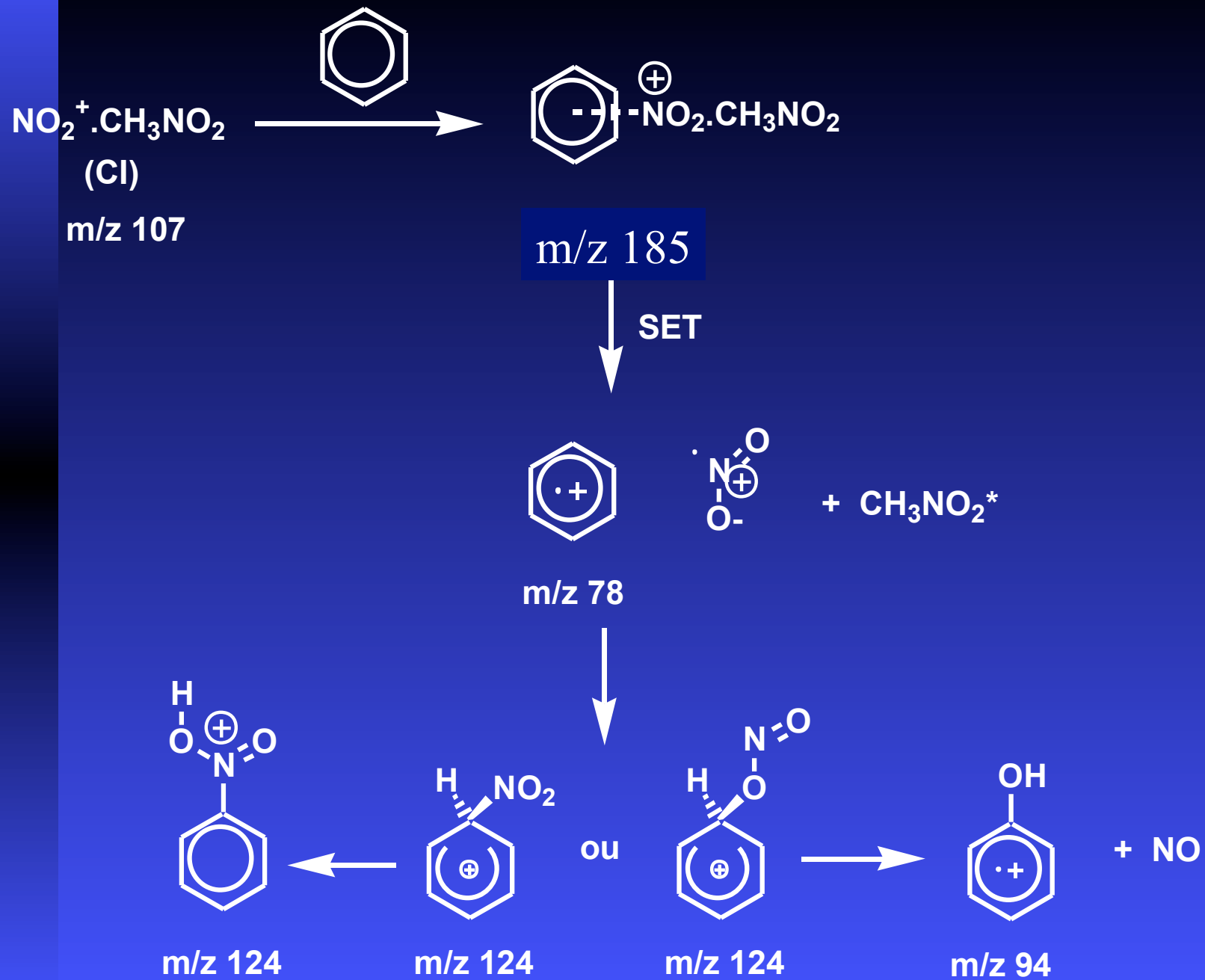
Reaction of Benzene with NO_2^+



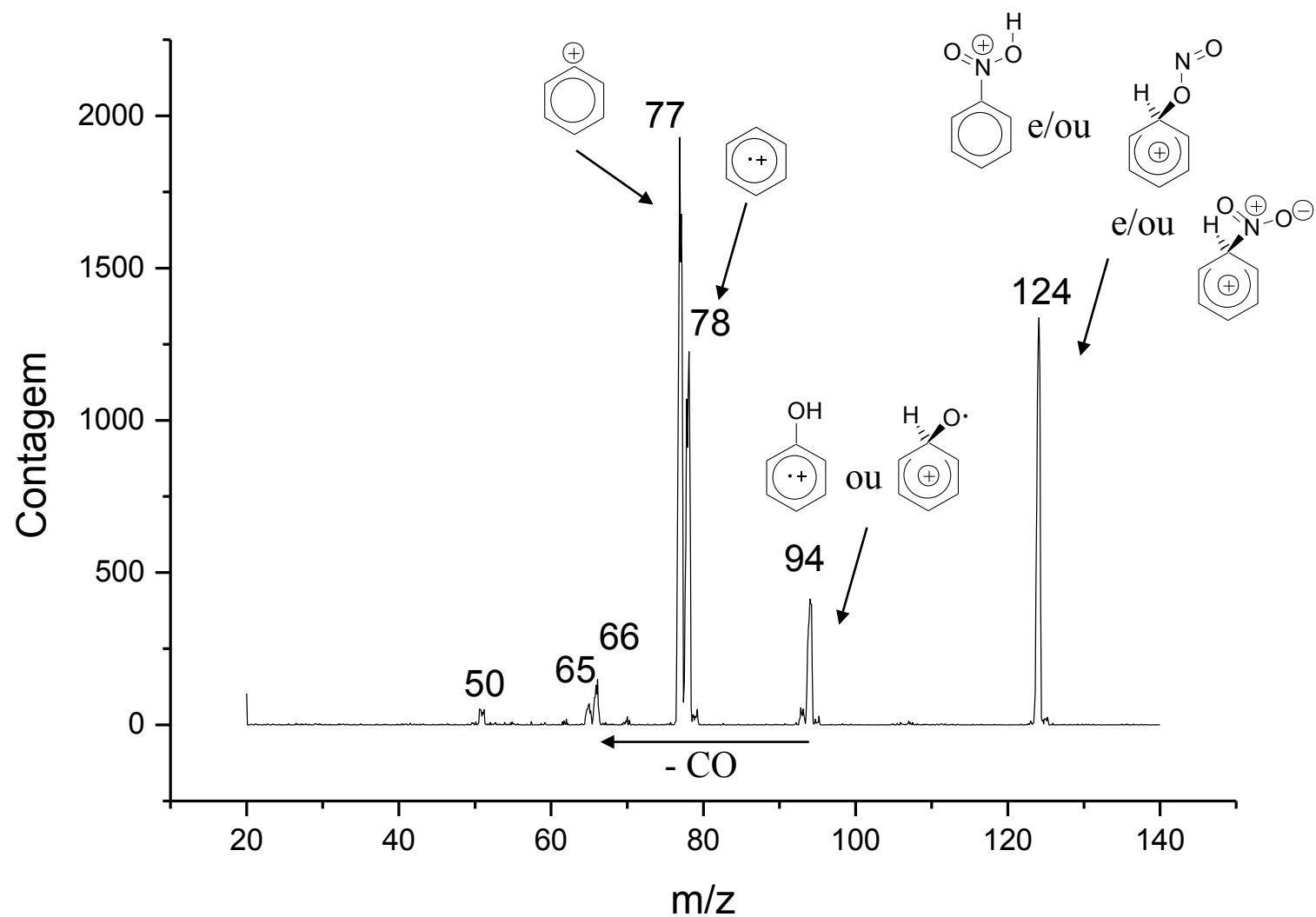
SET is dominant

Ion-Molecule Reaction: Solvent Effects



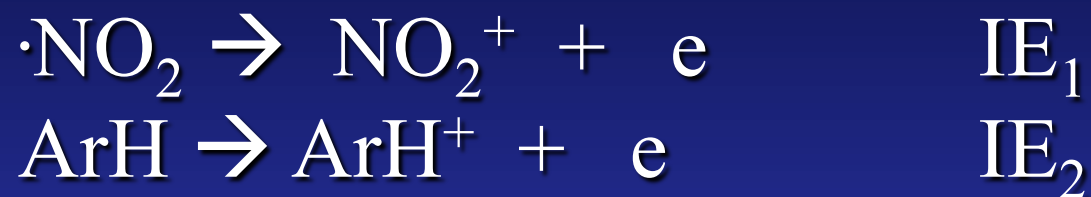


MS/MS of m/z 124



Does SET thermodynamically feasible?

Ionization Energy (Potential) for ionization in the Gas Phase

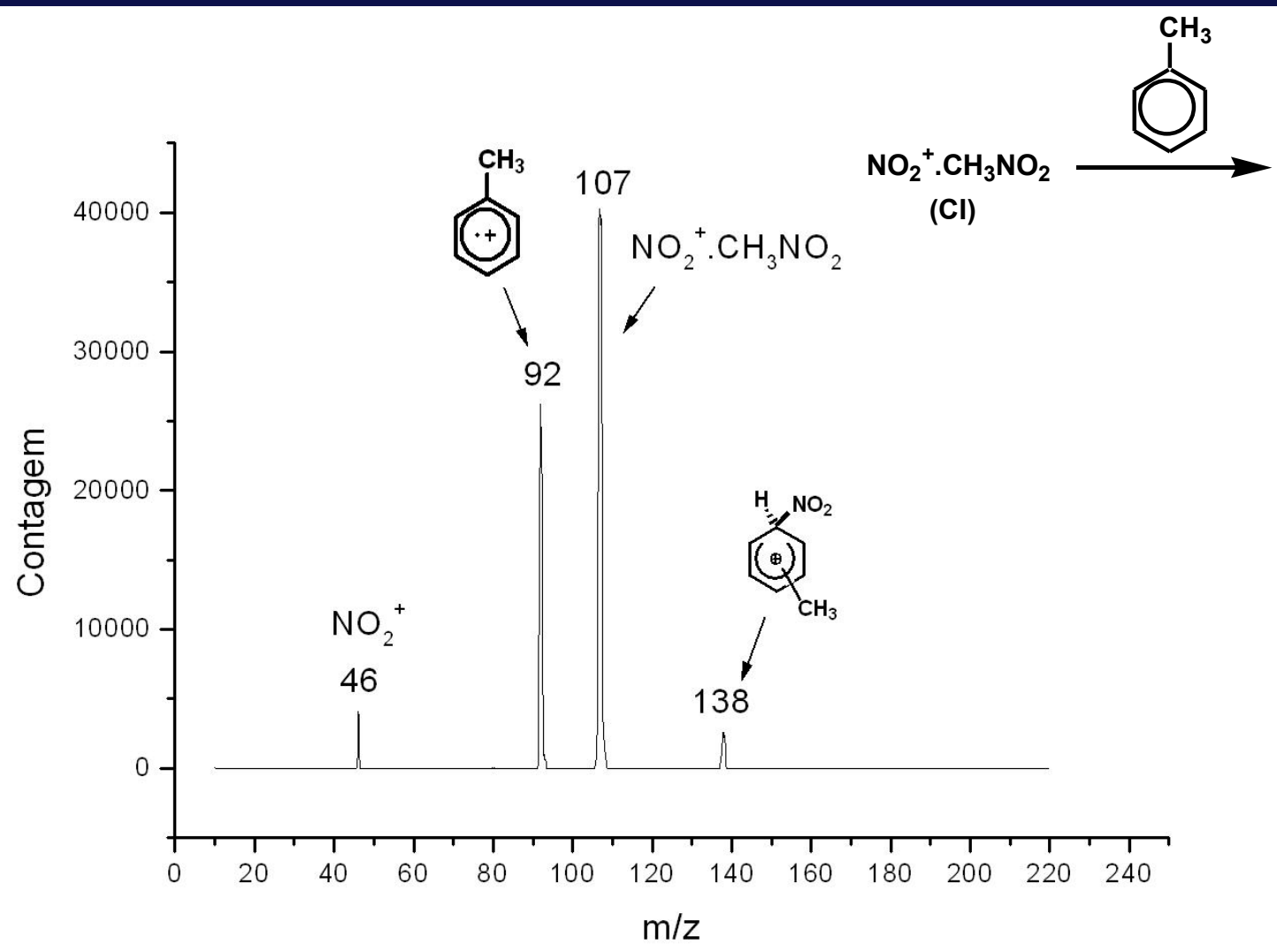


$$\Delta H_{\text{reaction}} \approx \text{IE}_2 - \text{IE}_1 = \Delta\text{IE}$$

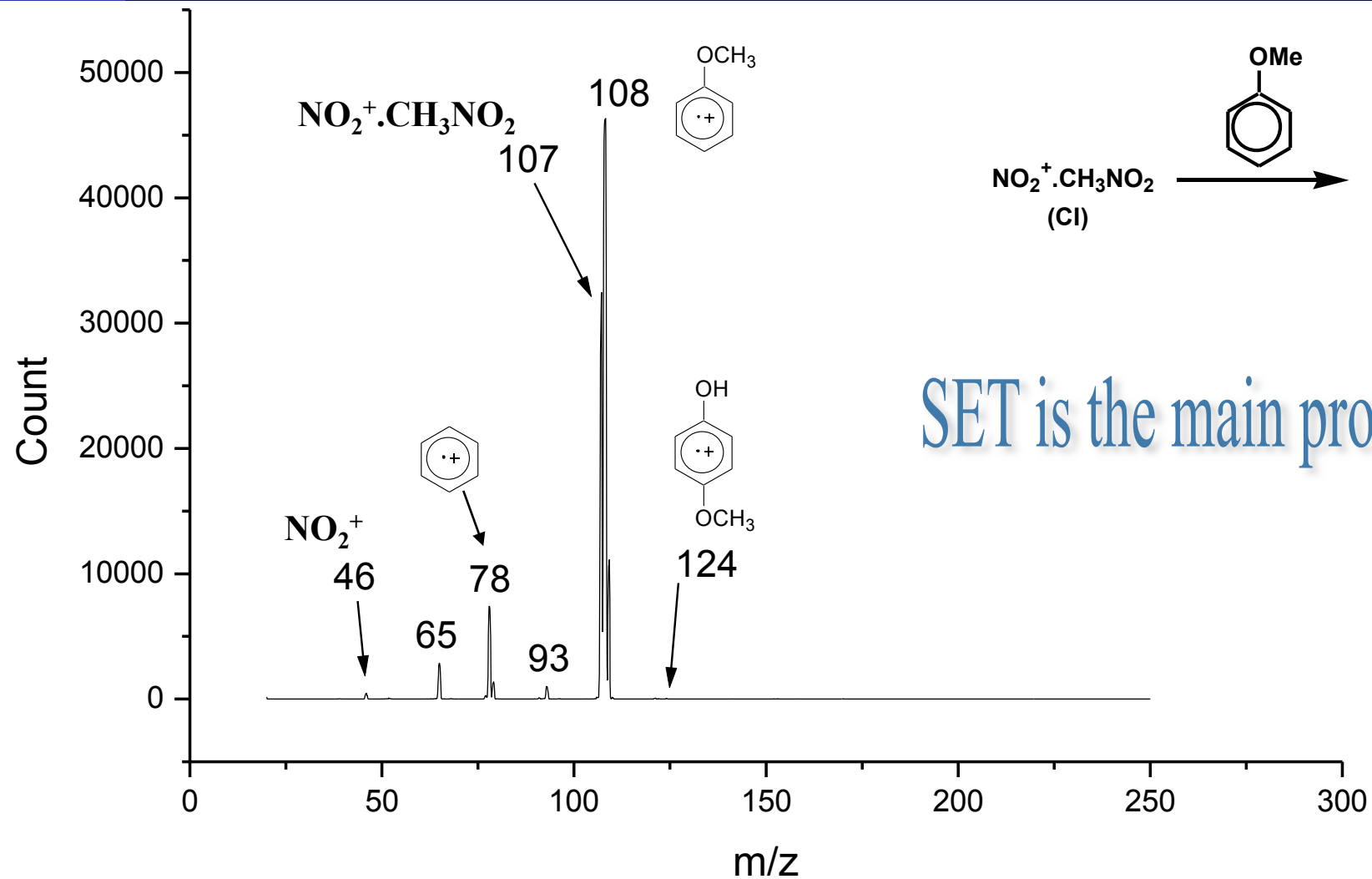
Substrate	Ionization Energy (IE) (eV)^a	ΔIE for Reaction with NO₂⁺ (eV)	ΔIE for Reaction with NO₂⁺ (kcal/mol)
NO ₂ → NO ₂ ⁺ + e	9.586 ± 0.002	0.000	0.00
Benzene → C ₆ H ₆ ⁺ + e	9.24378 ± 0.00007	-0.342	-7.89
Toluene → C ₇ H ₈ ⁺ + e	8.828 ± 0.001	-0.758	-17.48
mesitylene → C ₉ H ₁₂ ⁺ + e	8.40 ± 0.01	-1.186	-27.35
PhNH ₂ → PhNH ₂ ⁺ + e	7.720 ± 0.002	-1.866	-43.03
PhOMe → PhOMe ⁺ + e	8.20 ± 0.05	-1.386	-31.96
naphthalene → C ₁₀ H ₈ ⁺ + e	8.1442 ± 0.0009 8.141 ± 0.01	-1.442	-33.25
Nitrobenzene → C ₆ H ₅ NO ₂ ⁺ + e	9.94 ± 0.08	+0.354	+8.16
1,3-dinitrobenzene → C ₆ H ₄ N ₂ O ₄ ⁺ + e	10.4	+0.814	+18.77
C ₆ H ₅ CN → C ₆ H ₅ CN ⁺ + e	9.73 ± 0.01	+0.144	+3.32
C ₆ H ₅ CF ₃ → C ₆ H ₅ CF ₃ ⁺ + e	9.685 ± 0.005	+0.099	+2.28
fluorbenzene → C ₆ H ₅ F ⁺ + e	9.20 ± 0.01	-0.386	-8.90
chlorobenzene → C ₆ H ₅ Cl ⁺ + e	9.07 ± 0.02	-0.516	-11.9
bromobenzene → C ₆ H ₅ Br ⁺ + e	9.00 ± 0.03	-0.586	-13.5
iodobenzene → C ₆ H ₅ I ⁺ + e	8.72 ± 0.04	-0.866	-20.0

Data from NIST database: <http://webbook.nist.gov/chemistry>

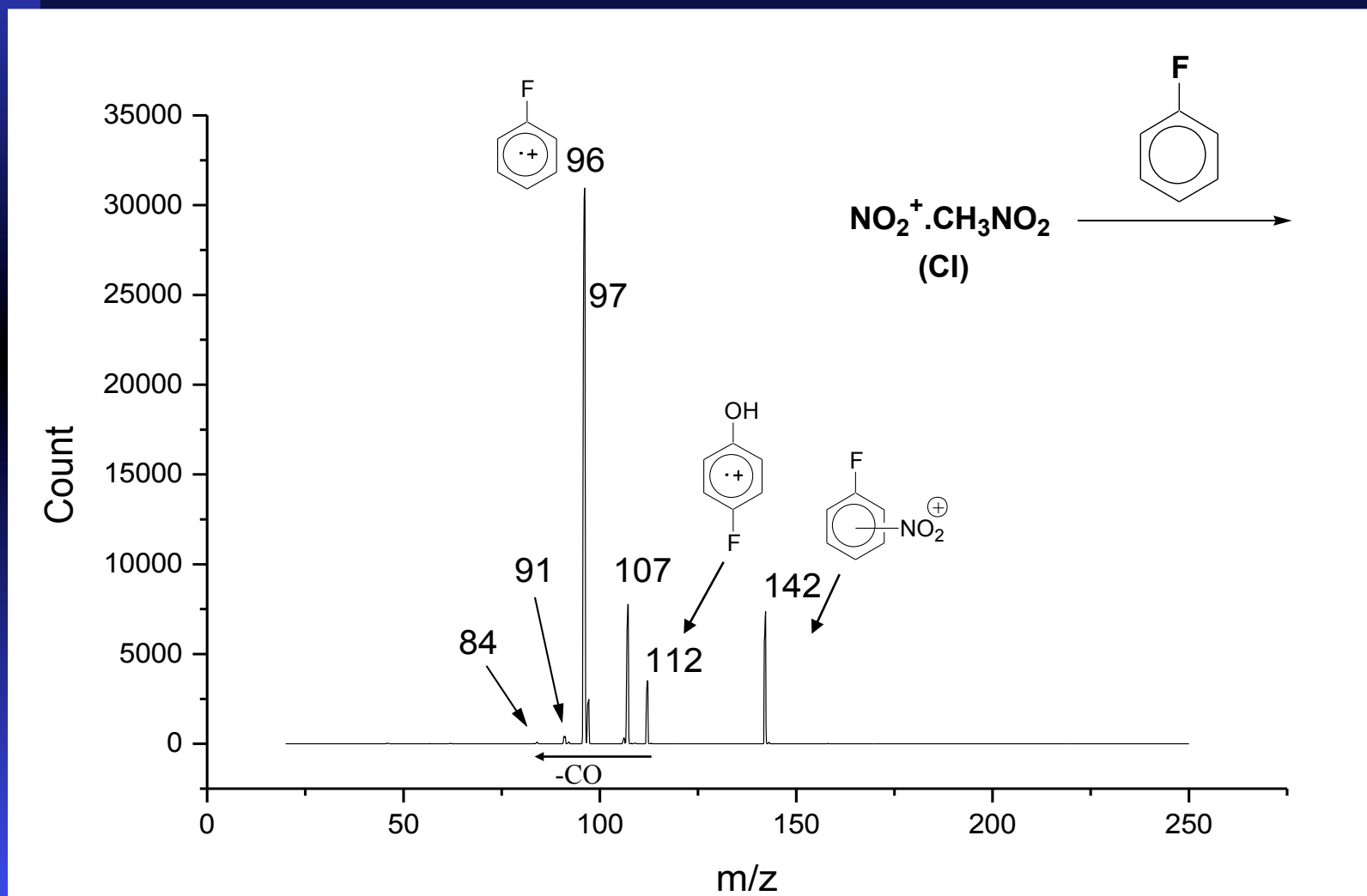
Nitration of Activated Aromatics



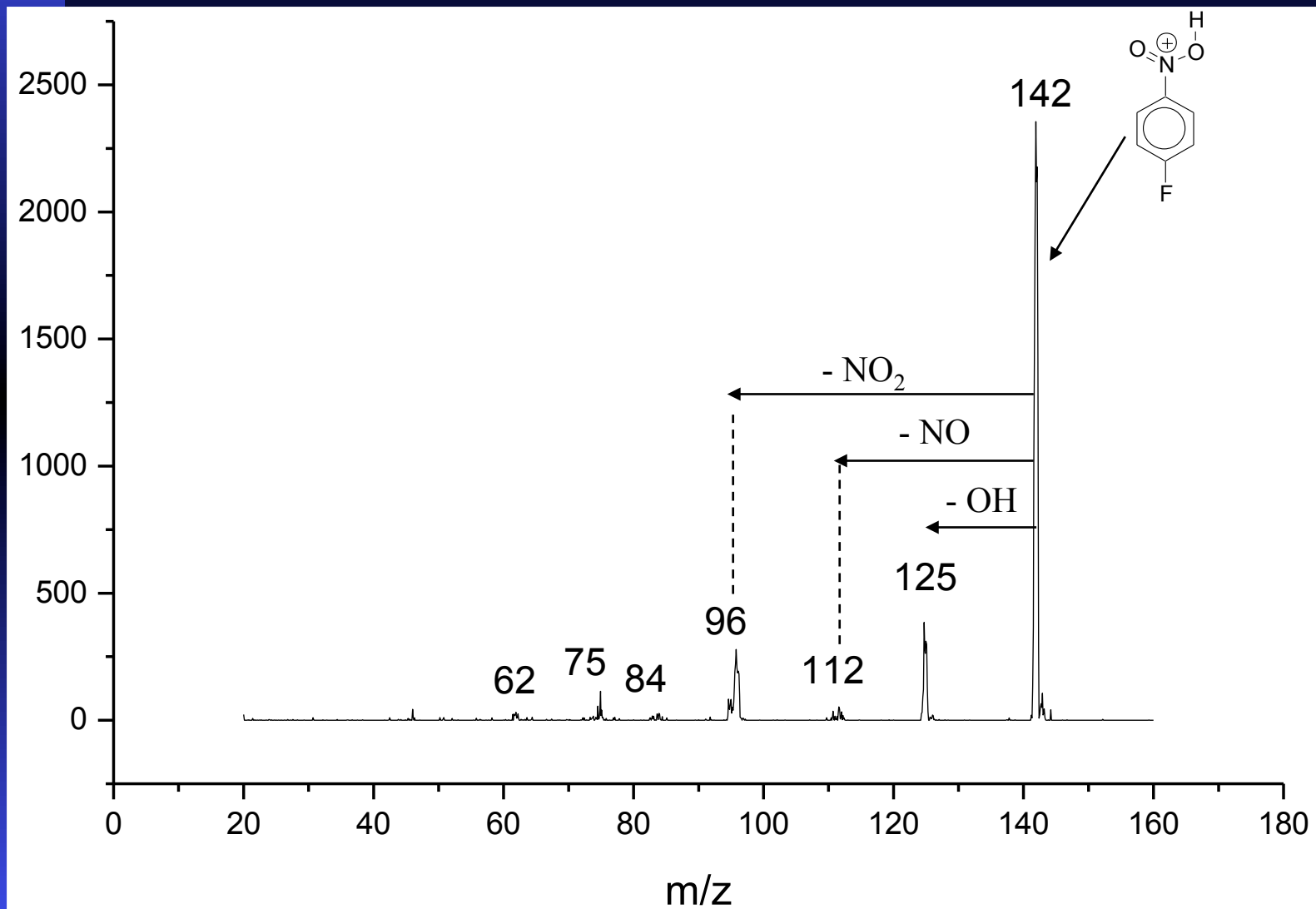
Nitration of Activated Aromatics



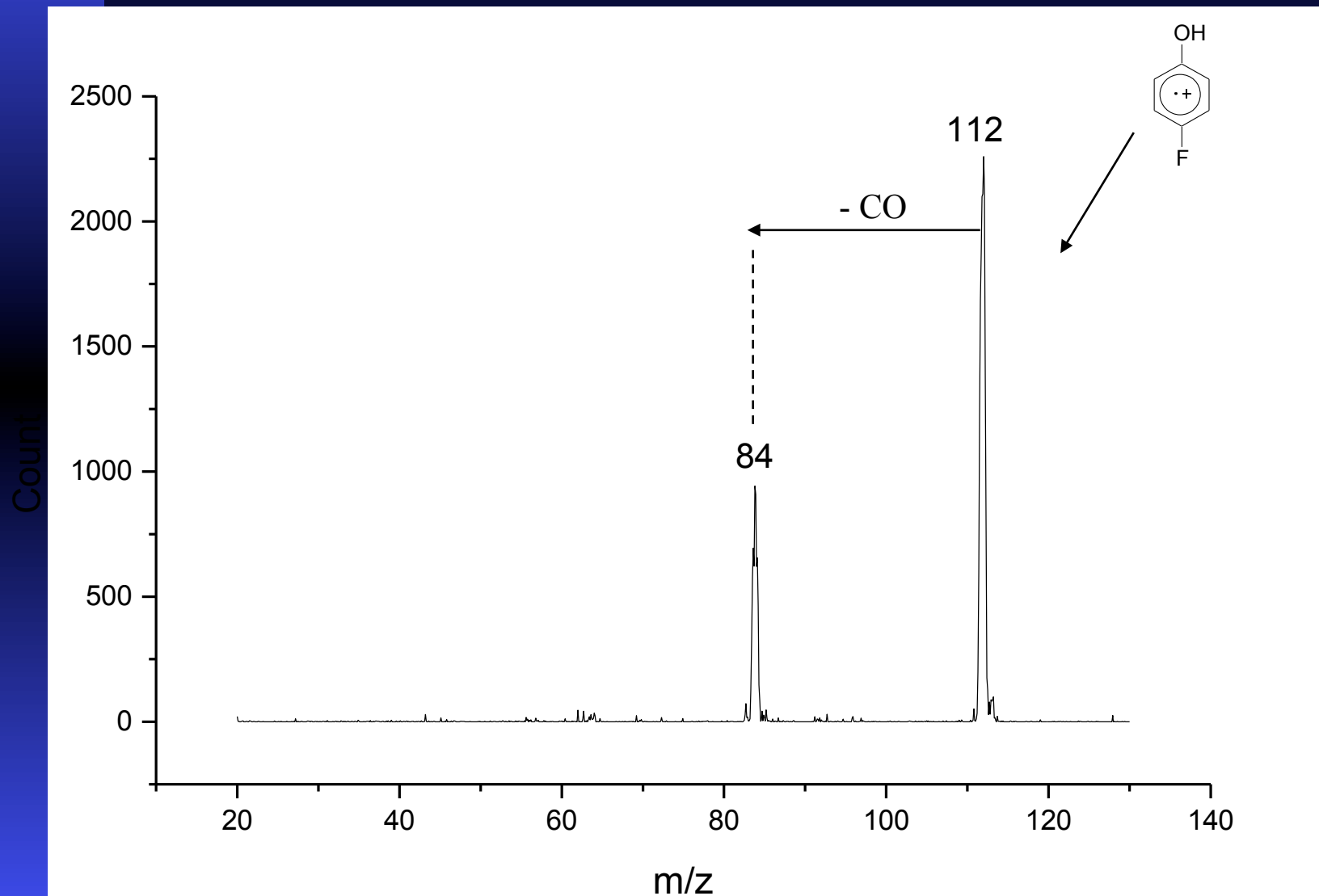
Nitration of Halo-Aromatics: PhF



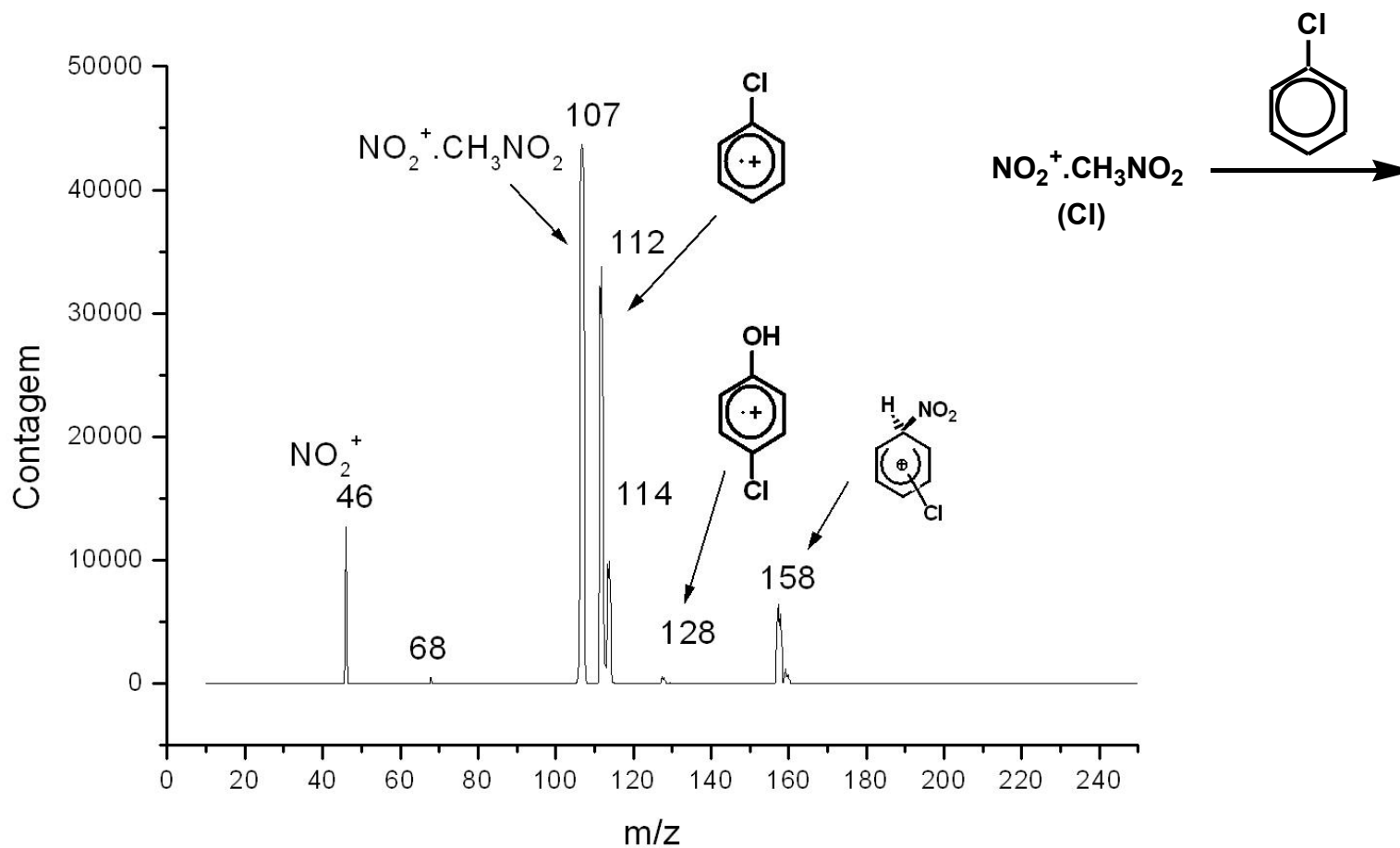
MS/MS of m/z 142



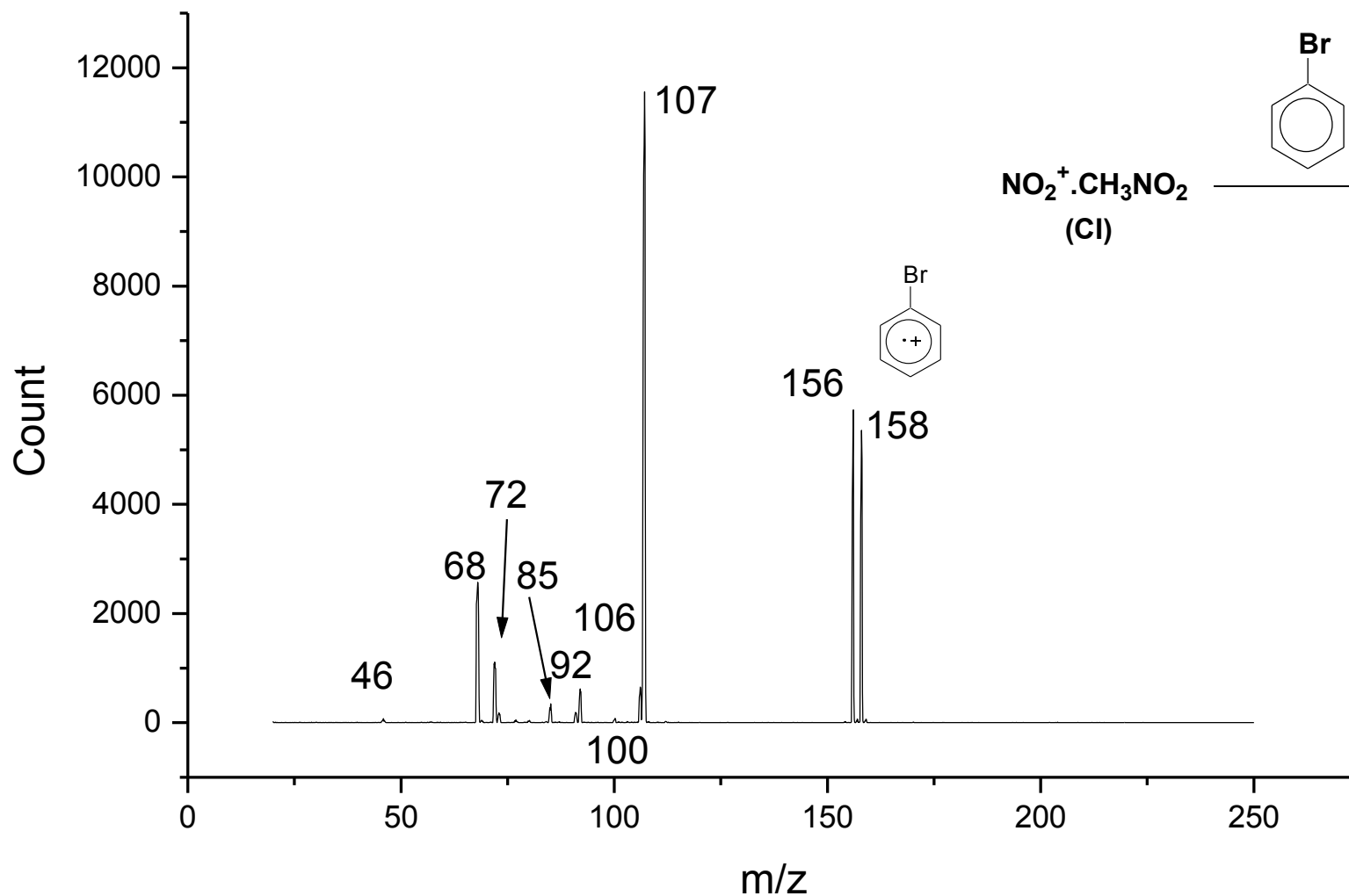
MS/MS of m/z 112



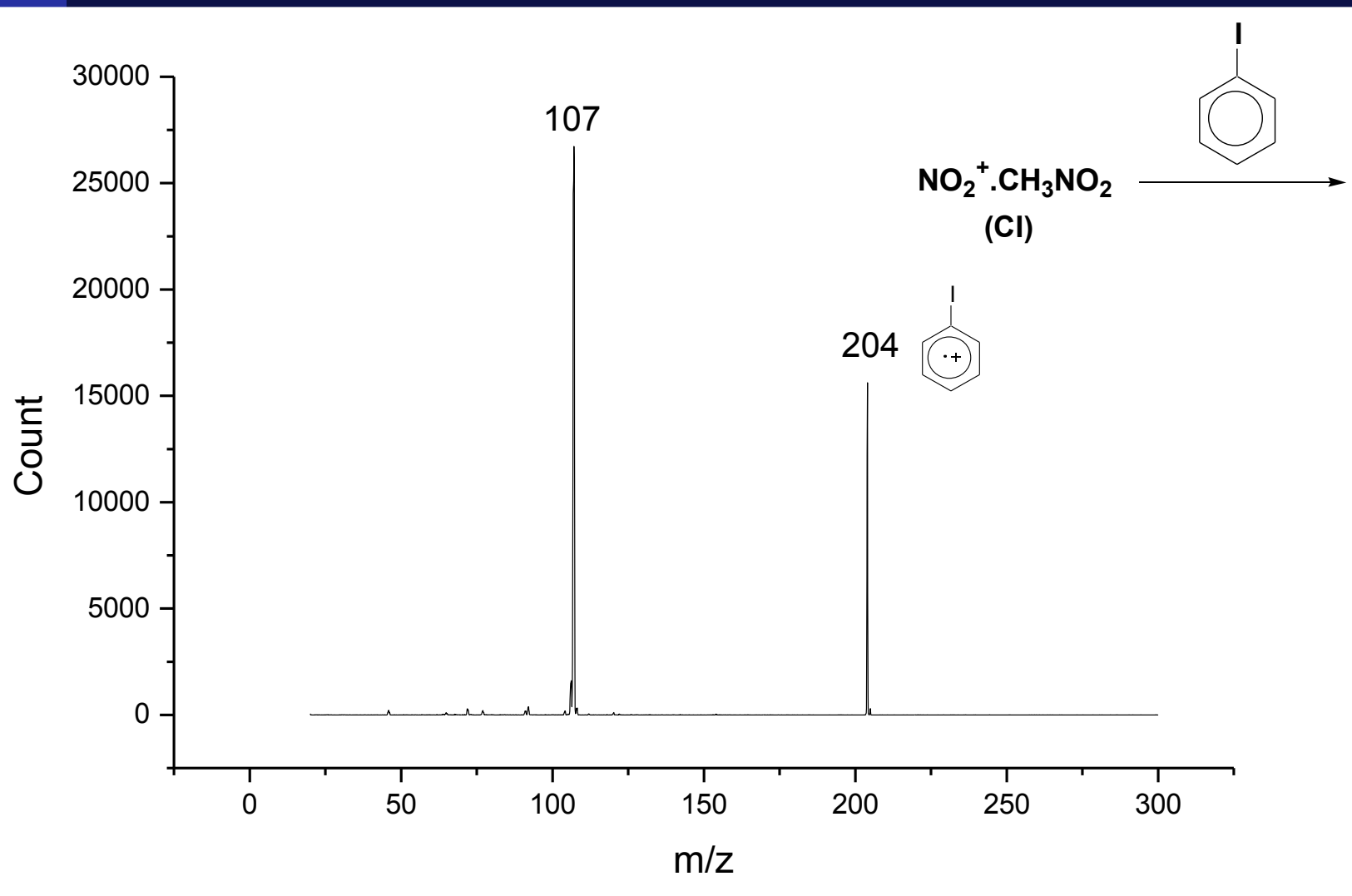
Nitration of Halo-Aromatics: PhCl



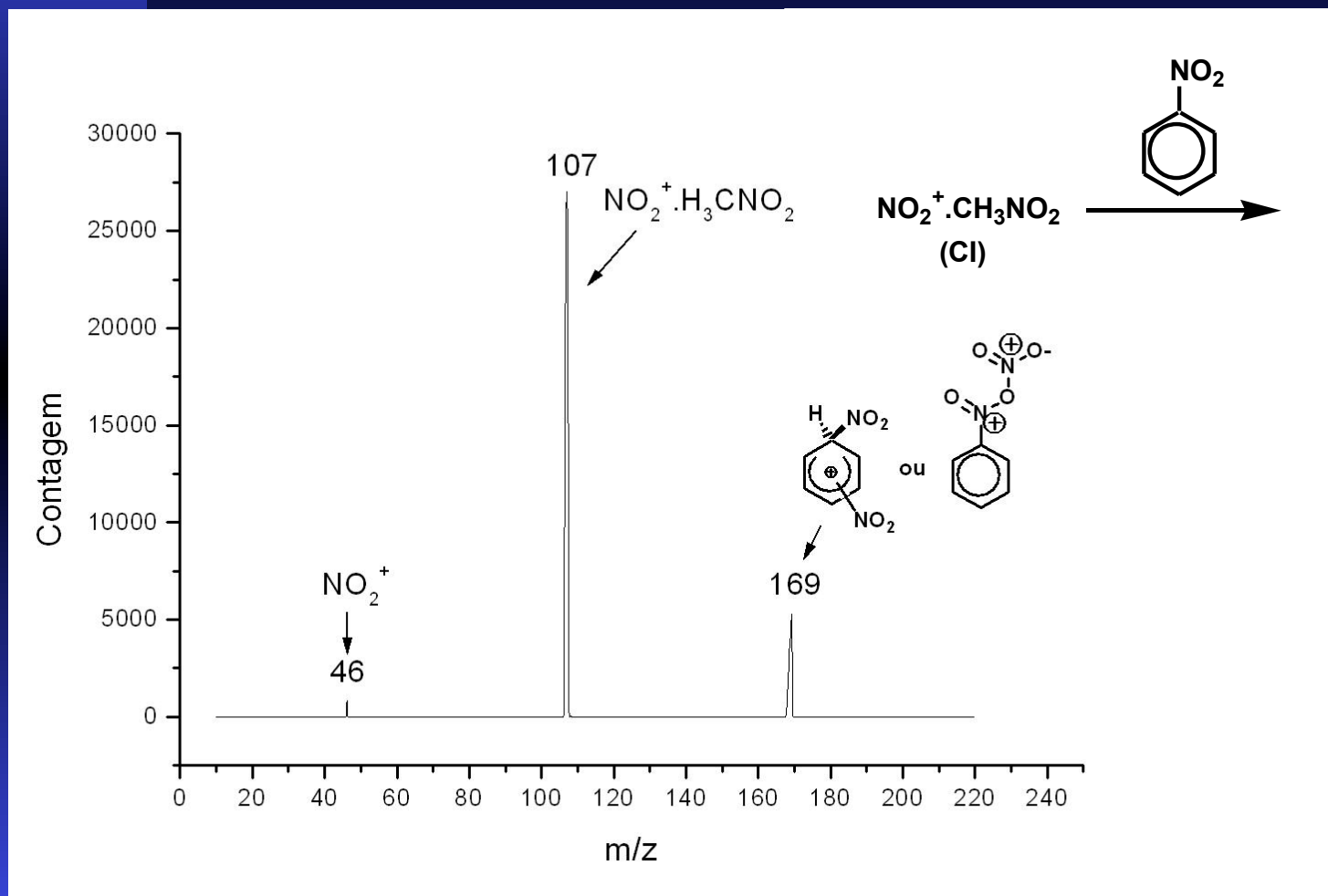
Nitration of Halo-Aromatics: PhBr



Nitration of Halo-Aromatics: PhI



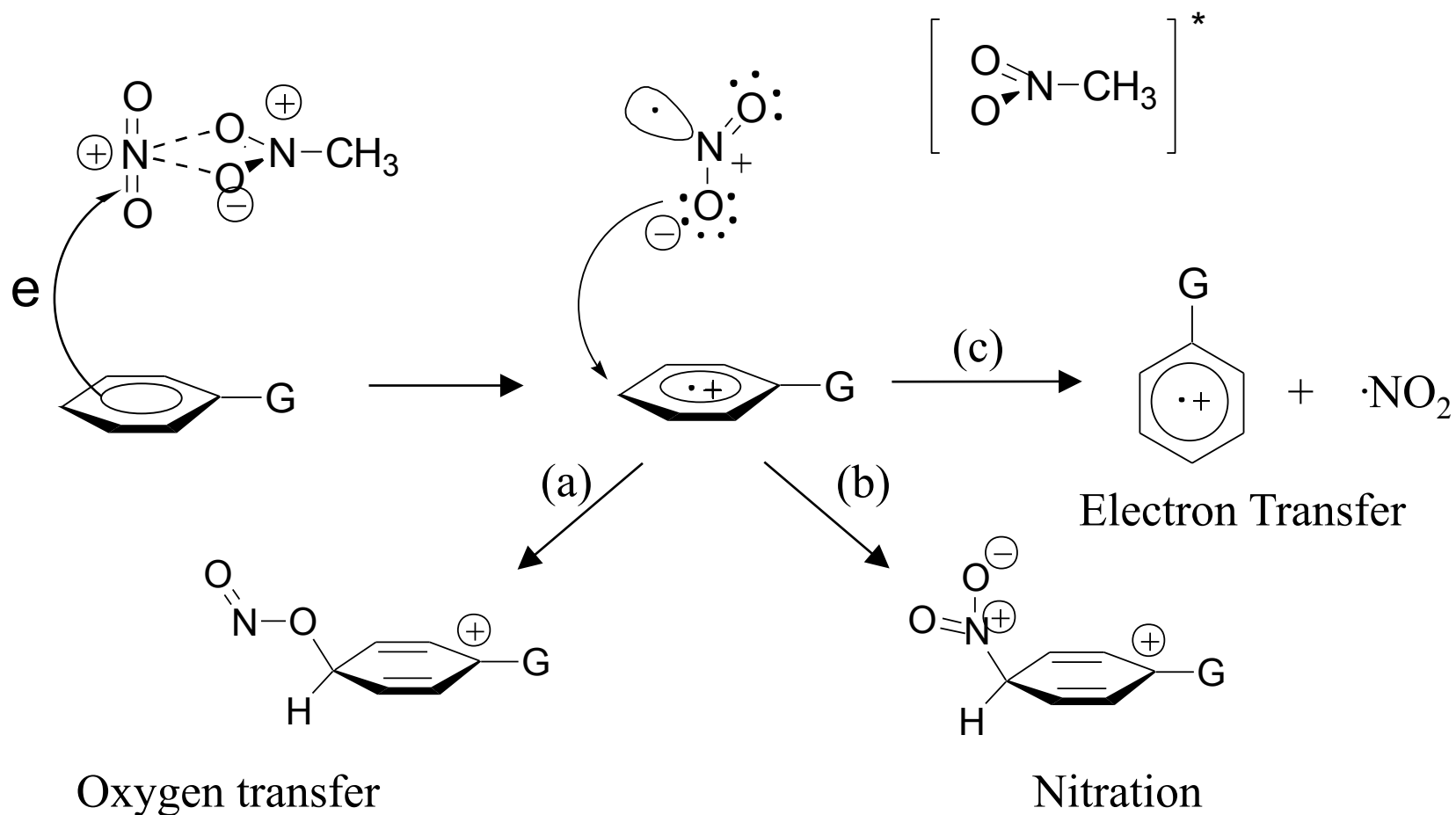
Nitration of Deactivated Aromatics



SET is not detected

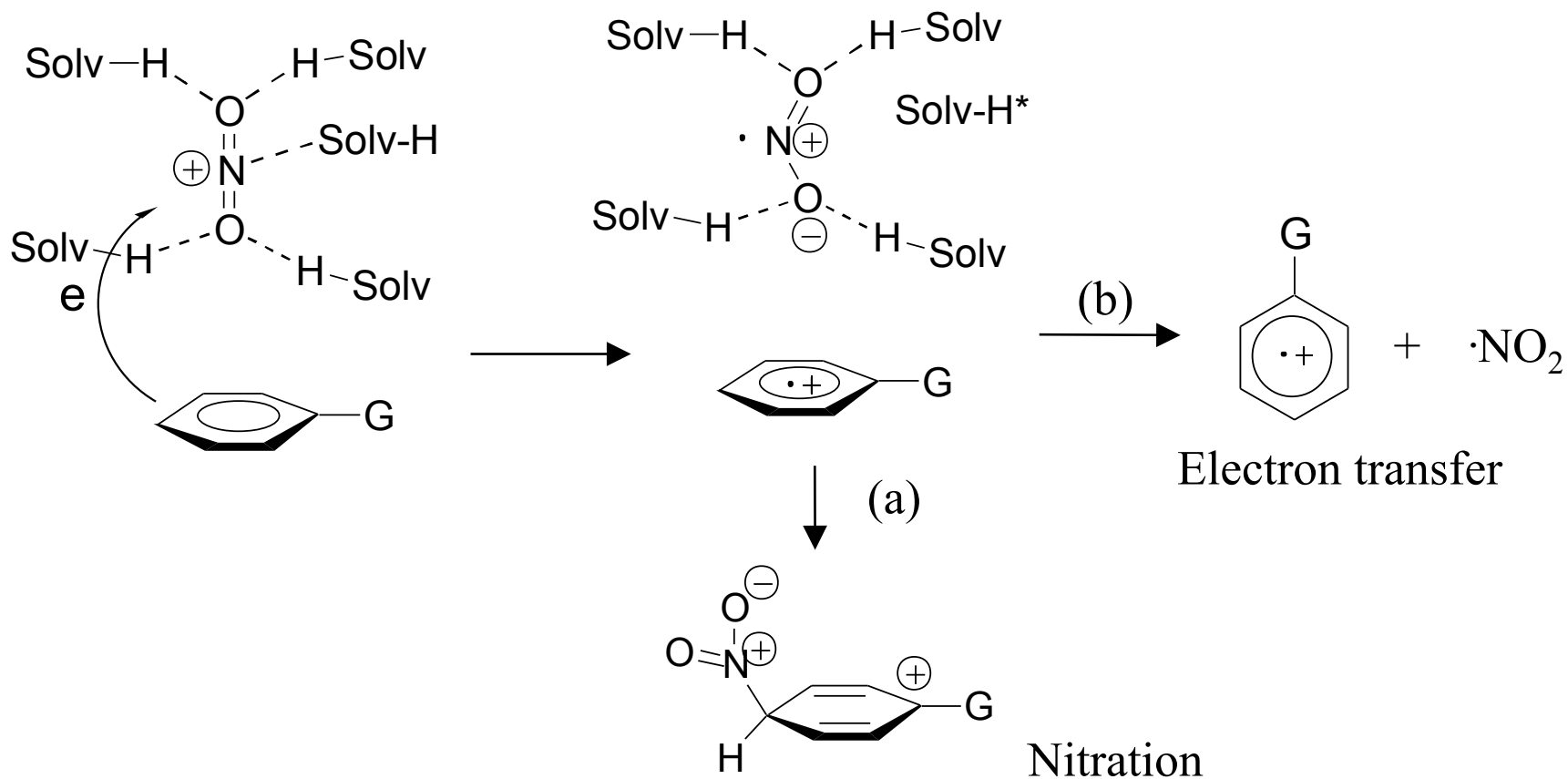
Proposal

■ Aprotic polar solvent

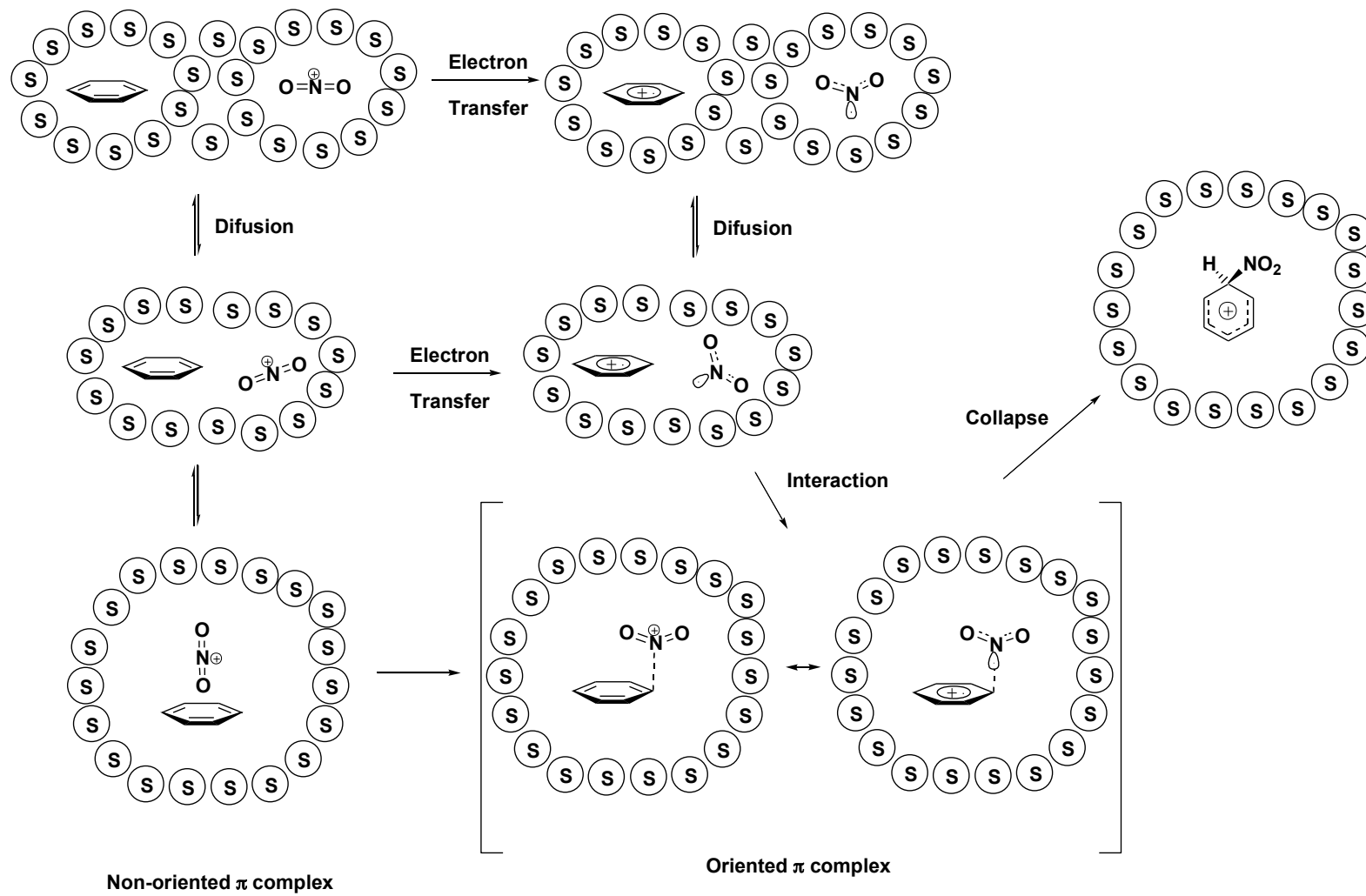


Proposal

■ Protic polar solvent

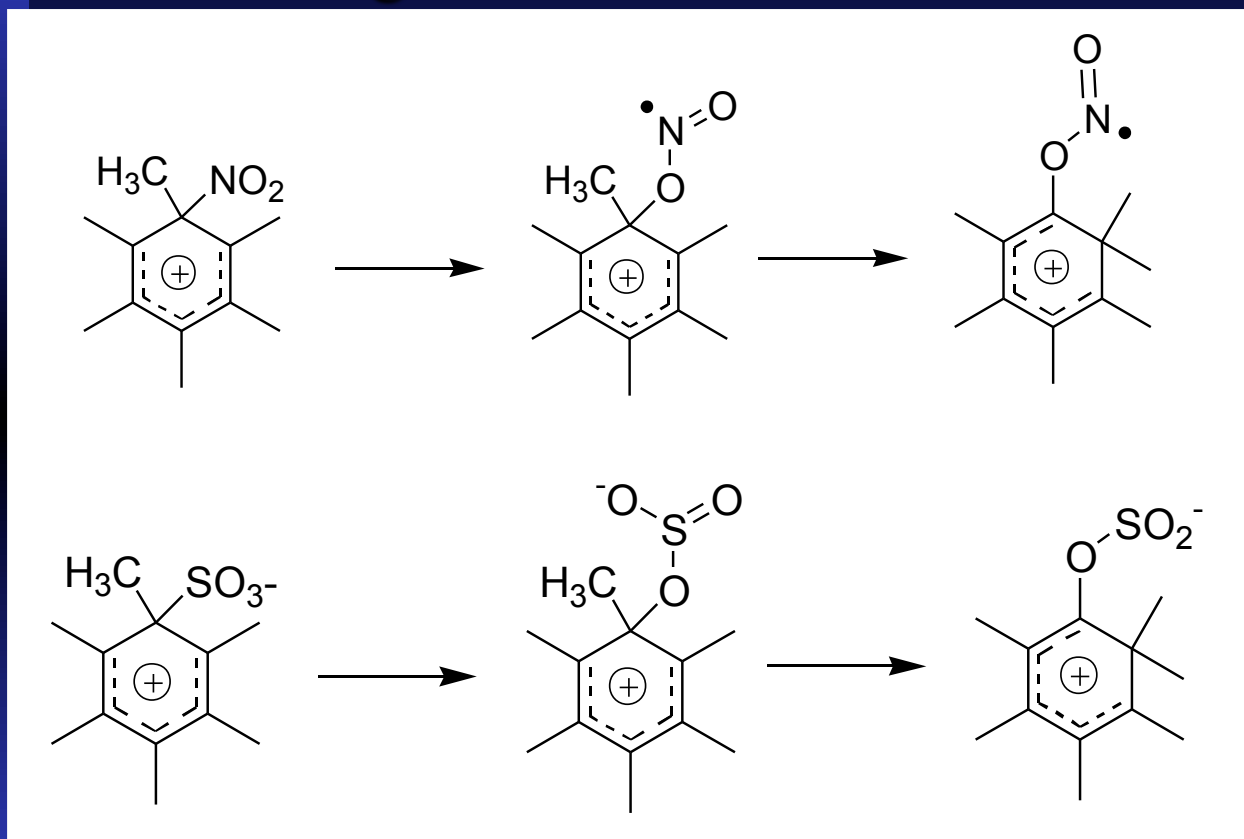


SET x Solvation



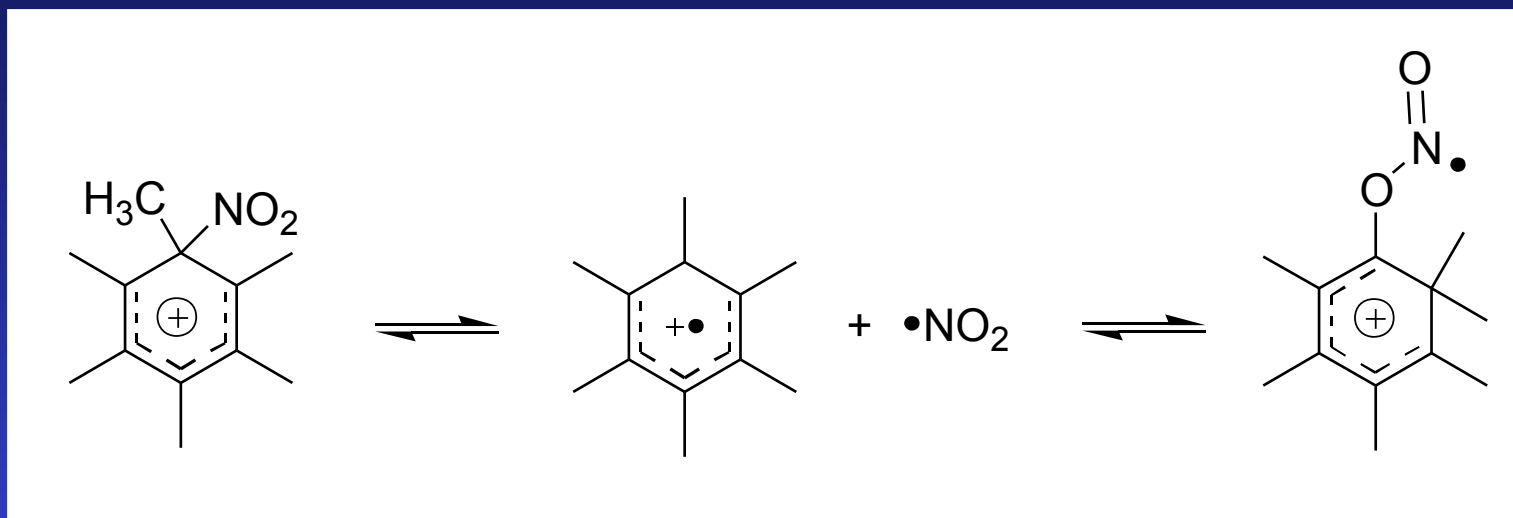
Easy to understand some “strange” behaviors

■ Rearrangements



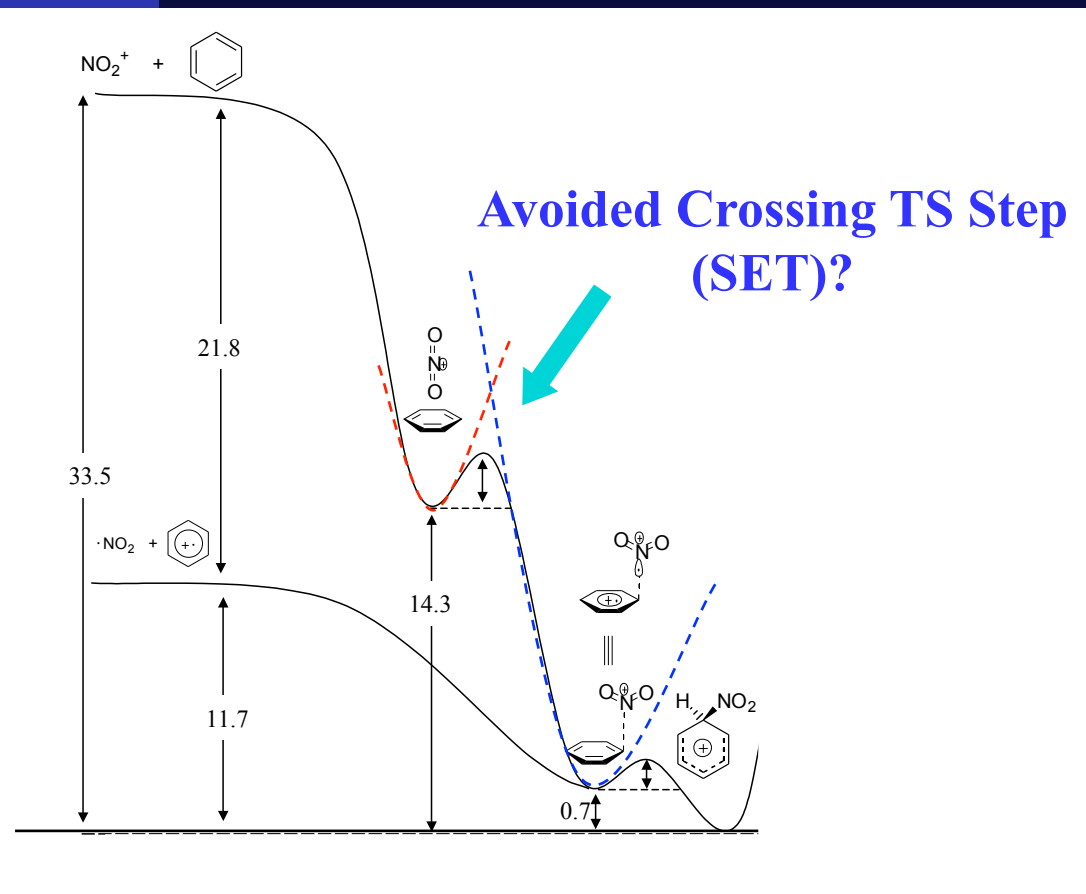
V. A. Koptug, *Top. Curr. Chem* **1984**, *122*, 1
Detsina and Koptug, *Zh. Org. Khim.* **1972**, *8*, 2158

^{18}O isotope study



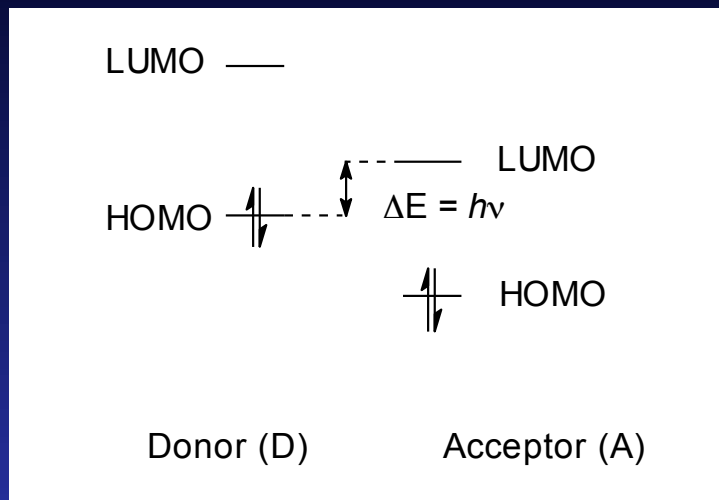
Detsina, Sidorova, Panova,
Malykhin, Shakirov
Zh. Org. Khim. 1979, 15, 1887

Proposal: Distinct Reaction Intermediates



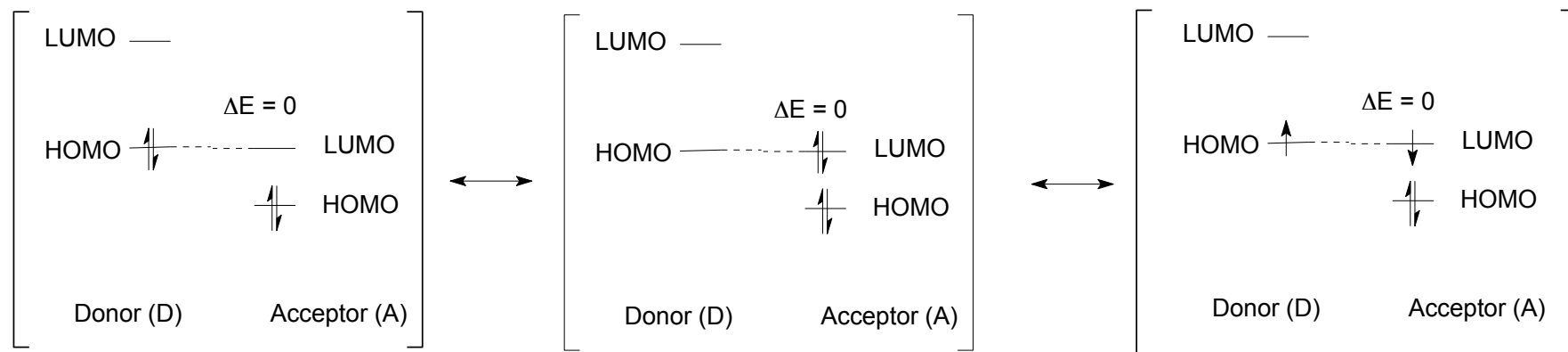
Three distinct intermediates before proton elimination

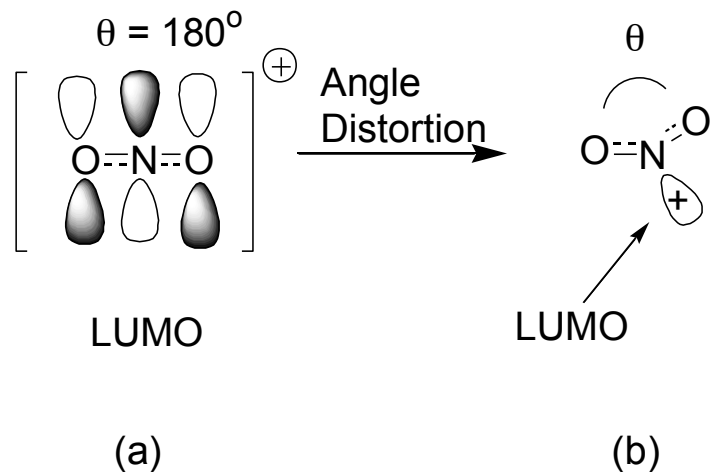
Frontier MO and its relation to SET



(a) Ground State: $|\text{NO}_2^+, \text{C}_6\text{H}_6\rangle$

(b) Ground State: $c_1 |\text{NO}_2^+, \text{C}_6\text{H}_6\rangle + c_2 |\text{NO}_2, \text{C}_6\text{H}_6^+\rangle + \dots$

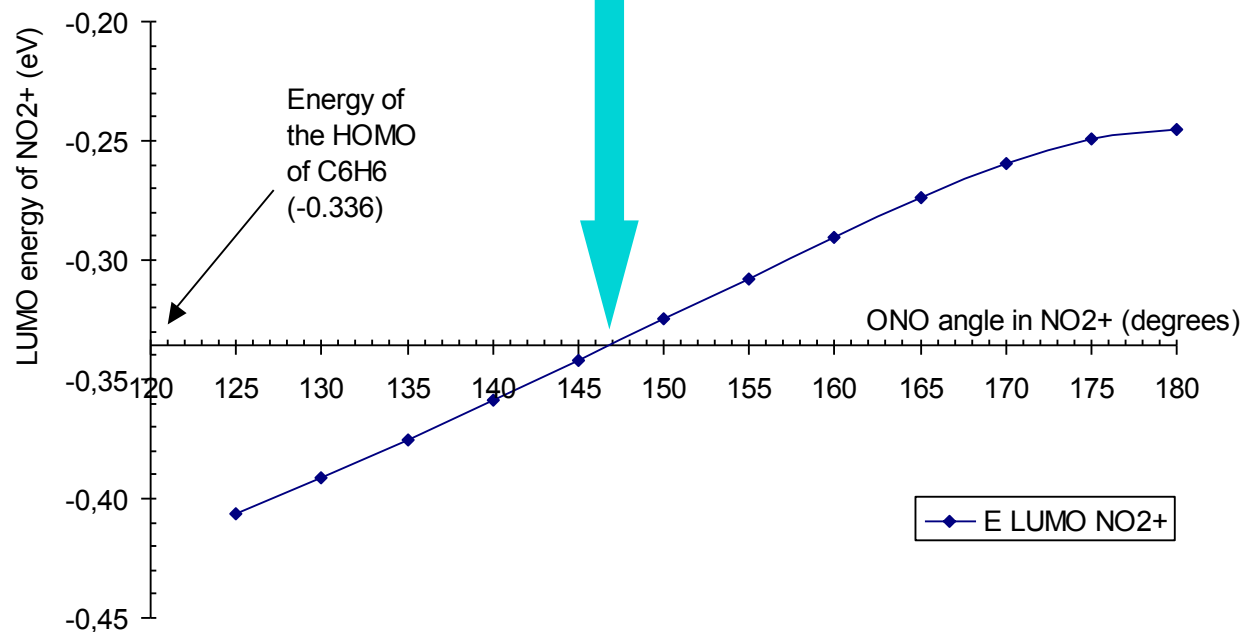




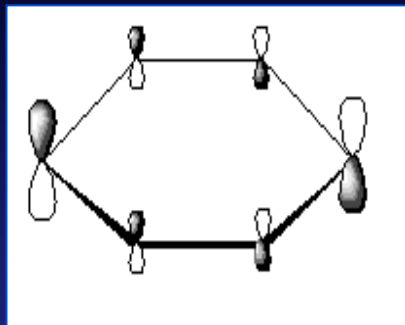
LUMO in NO_2^+ cation at (a) linear and (b) bent geometries.

**HOMO (ArH)-LUMO (NO_2^+)
Crossing point
(approximate geometry where SET takes place)**

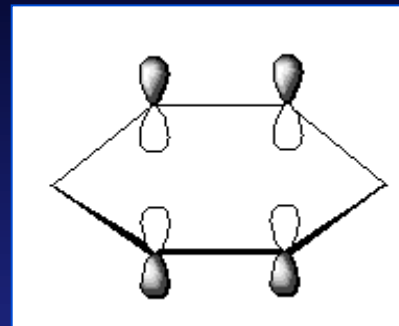
LUMO energy of NO_2^+ as a function of the ONO bond angle. The LUMO of NO_2^+ becomes isoenergetic with the HOMO of benzene at 147° , indicating an approximate geometry for the SET process.



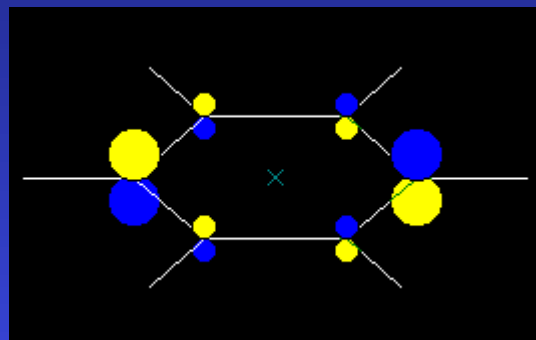
HOMO of Benzene



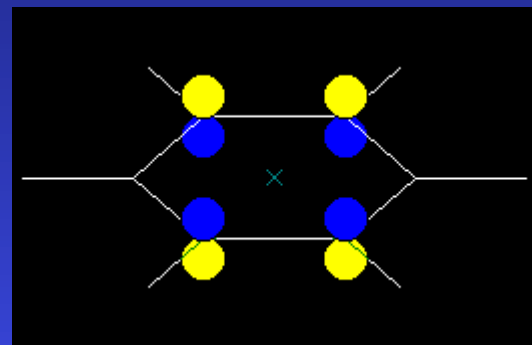
Symmetric



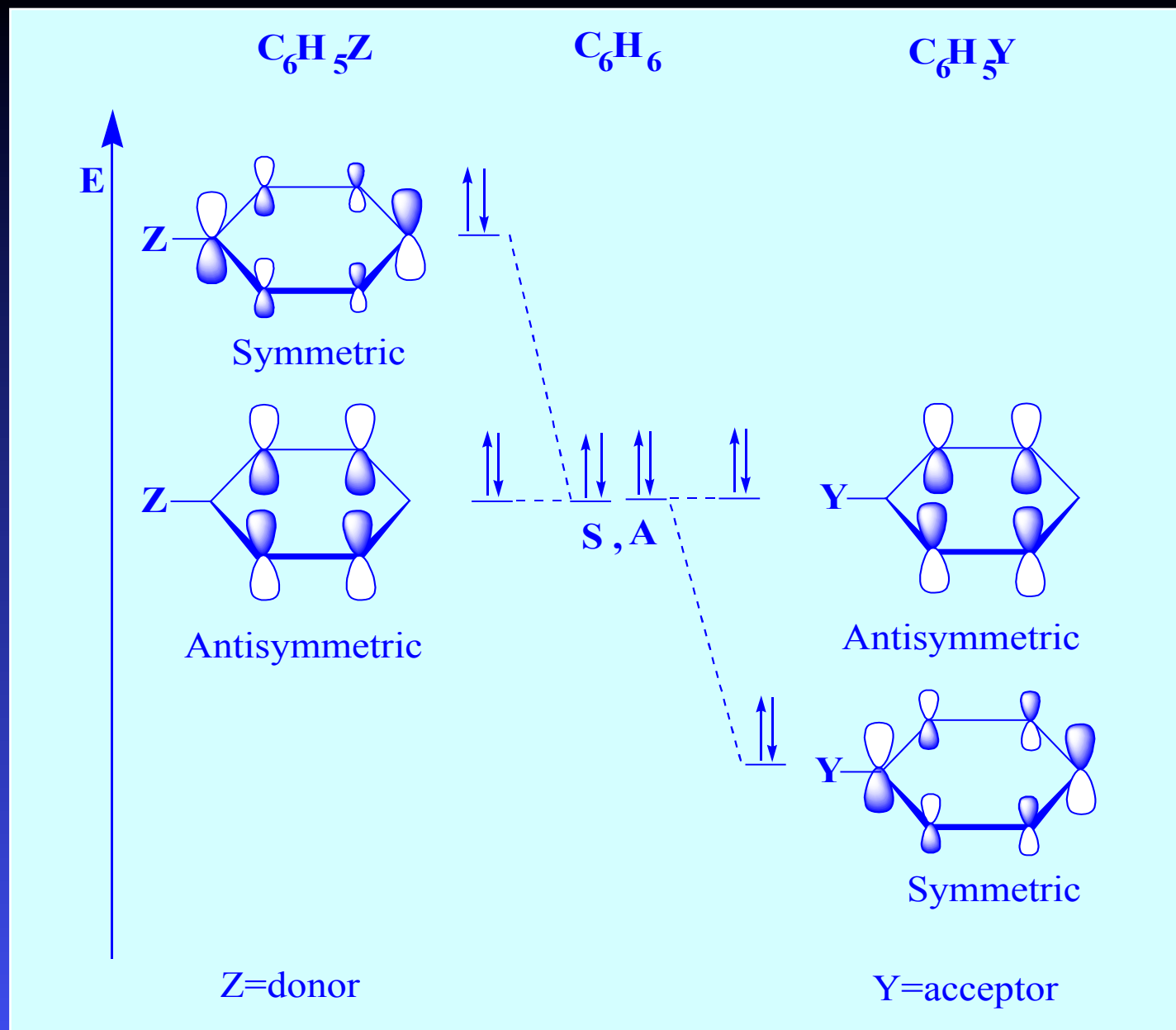
Antisymmetric



$E = -0,329$ Hartrees



$E = -0,329$ Hartrees



Fukuzumi, S.; Kochi, J.K.; J. Am. Chem. Soc., 103,7240, 1981.

Energy (a.u.) of MO's for the aromatic substrates

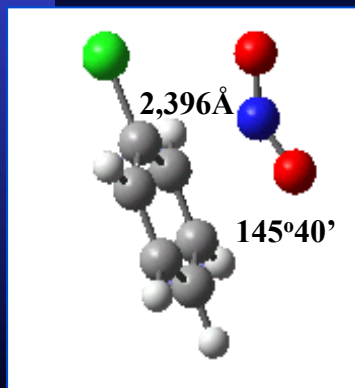
Substrate	HOMO	HOMO - 1
Benzene	-0,329 (S)	-0,329 (A)
Toluene	-0,317 (S)	-0,328 (A)
Aniline	-0,290 (S)	-0,330 (A)
Phenol	-0,310 (S)	-0,338 (A)
Fluorbenzene	-0,334 (S)	-0,347 (A)
Clorobenzene	-0,333 (S)	-0,347 (A)
Bromobenzene	-0,330 (S)	-0,348 (A)
Nitrobenzene	-0,365 (A)	-0,374 (S)
Benzaldehyde	-0,346 (A)	-0,350 (S)
(Trifluormethyl)benzene	-0,352 (A)	-0,357 (S)

Analysis of symmetry and energy of selected MOs

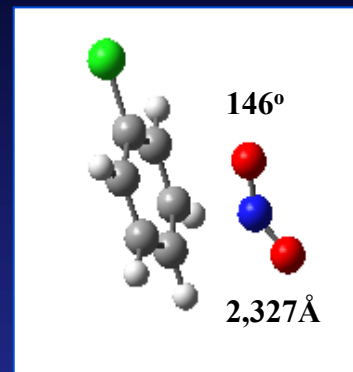
Donors: CH₃, NH₂, OH, F, Cl and Br.

Acceptors: NO₂, CHO and CF₃.

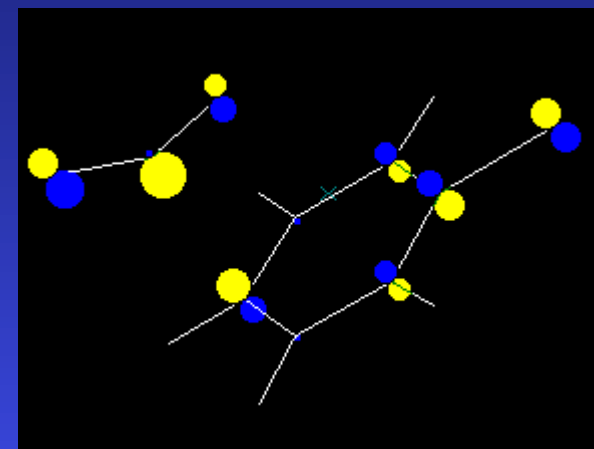
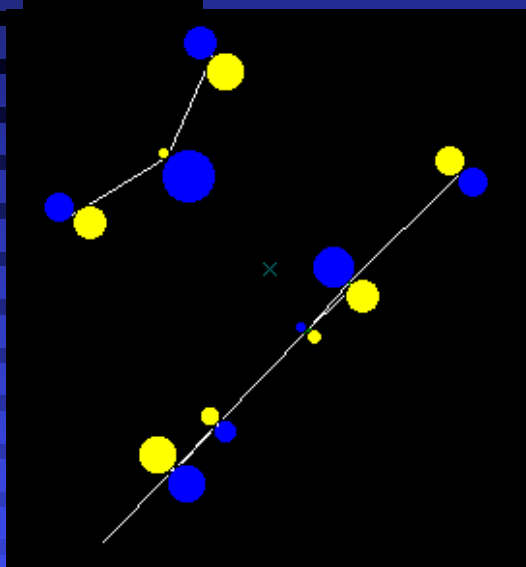
Regioselectivity: SET pair for PhCl



$$q(\text{NO}_2) = +0.34 e^-$$
$$q(\text{ArH}) = +0.66 e^-$$



$$q(\text{NO}_2) = +0.30 e^-$$
$$q(\text{ArH}) = +0.70 e^-$$



Directing groups ortho and para

SET complex is only formed at ipso and para positions

MO's for the complex between PhNO_2 and NO_2^+

ortho

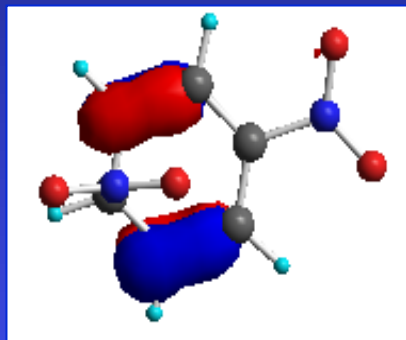


HOMO

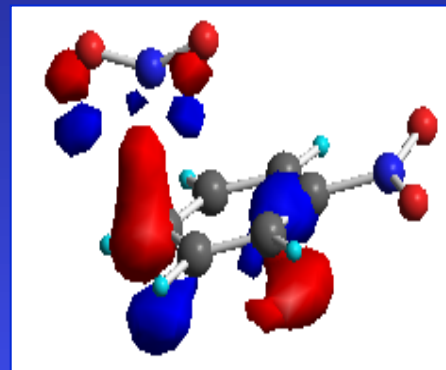


HOMO - 1

para

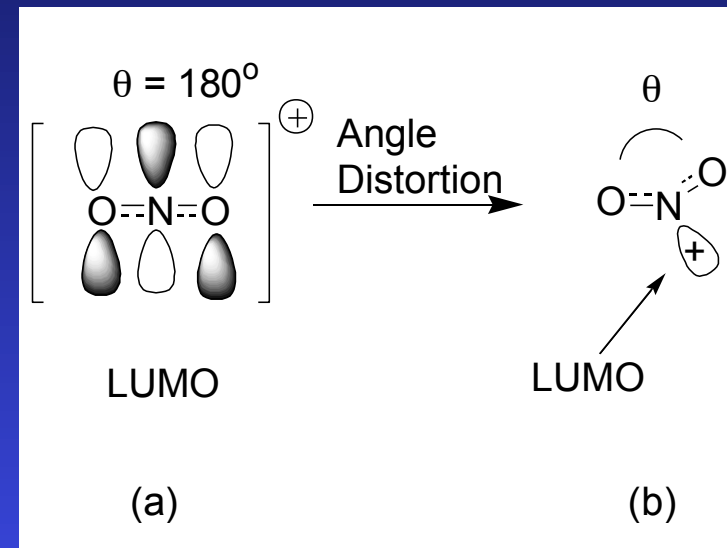
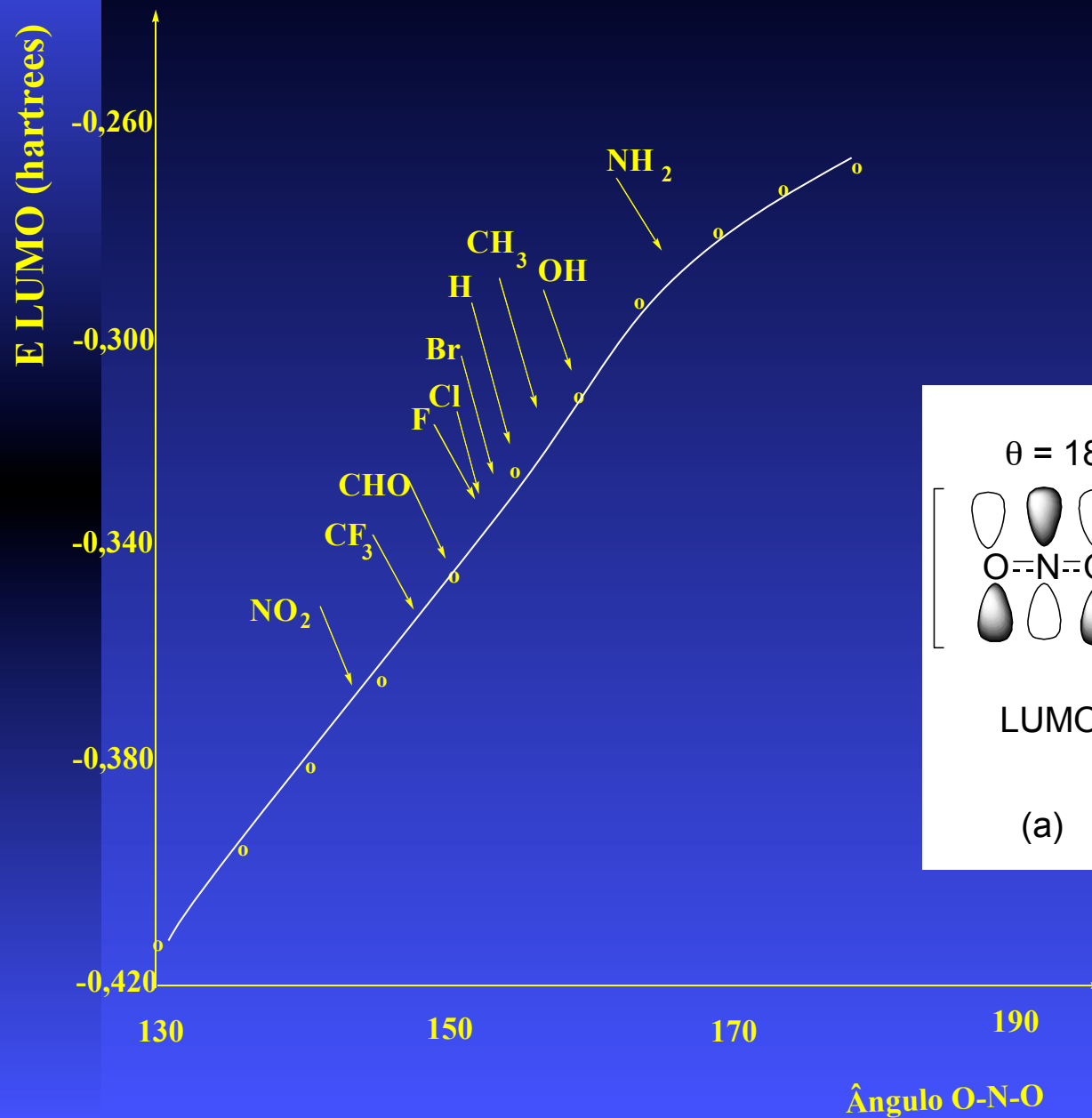


HOMO

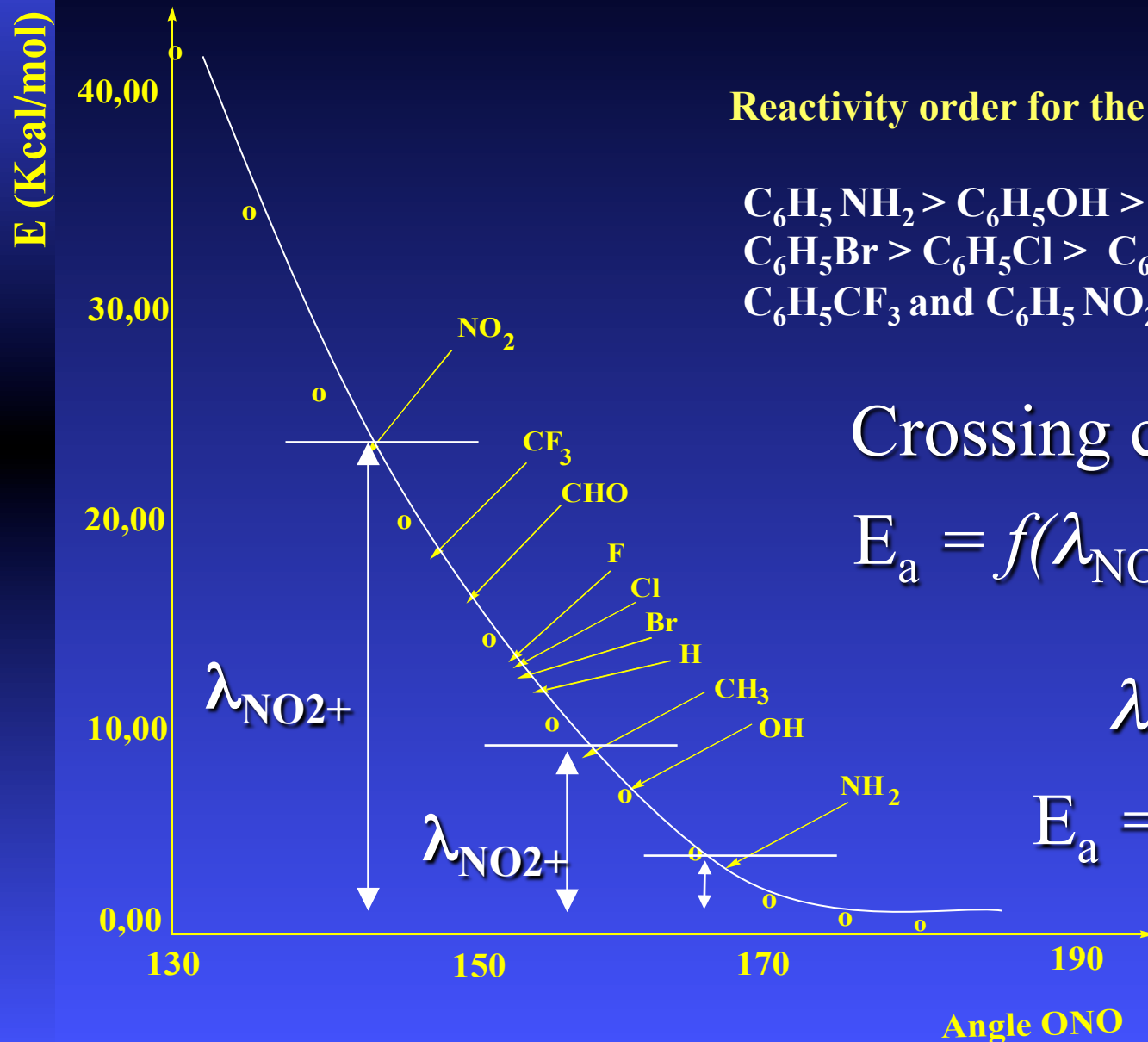


HOMO - 1

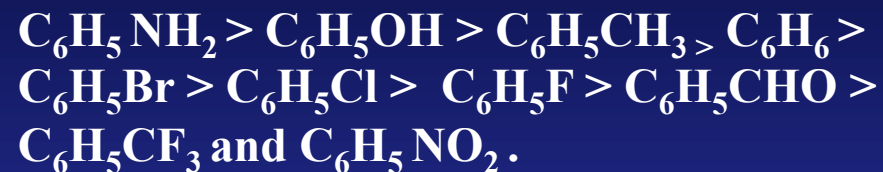
E_{LUMO} of NO_2^+ versus θ_{ONO}



E_{rel} of NO_2^+ (λ_{Marcus}) versus θ_{ONO}



Reactivity order for the substrates:



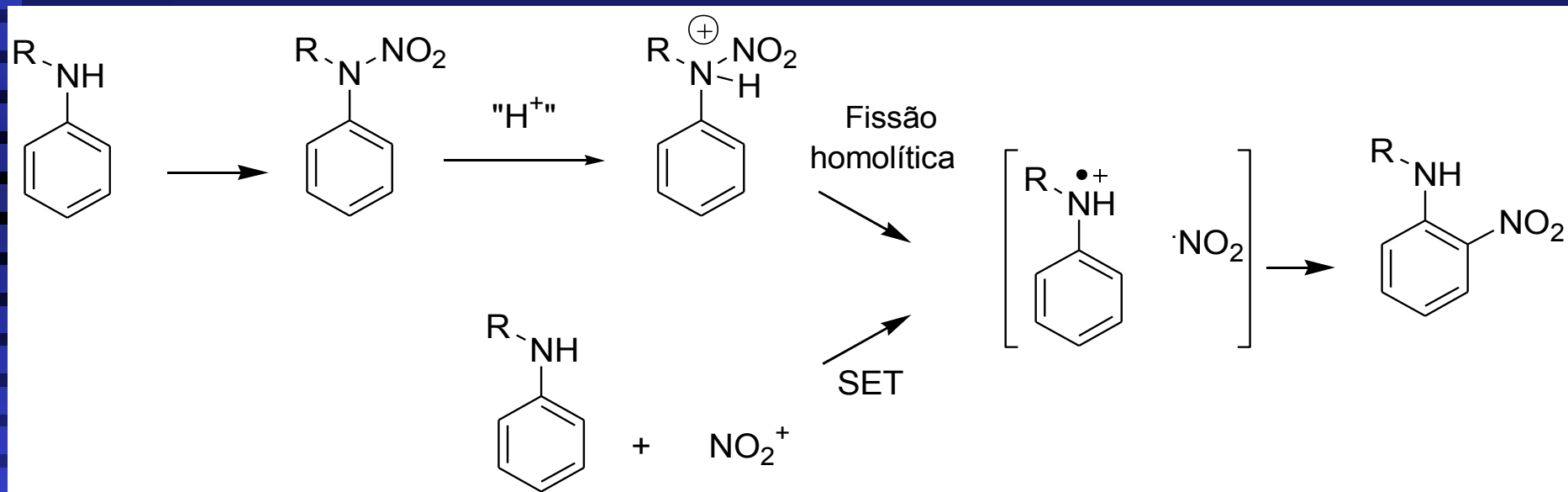
Crossing curve model

$$E_a = f(\lambda_{\text{NO}_2^+} + \lambda_{\text{ArH}})$$

$$\lambda_{\text{ArH}} \approx 0$$

$$E_a = f(\lambda_{\text{NO}_2^+})$$

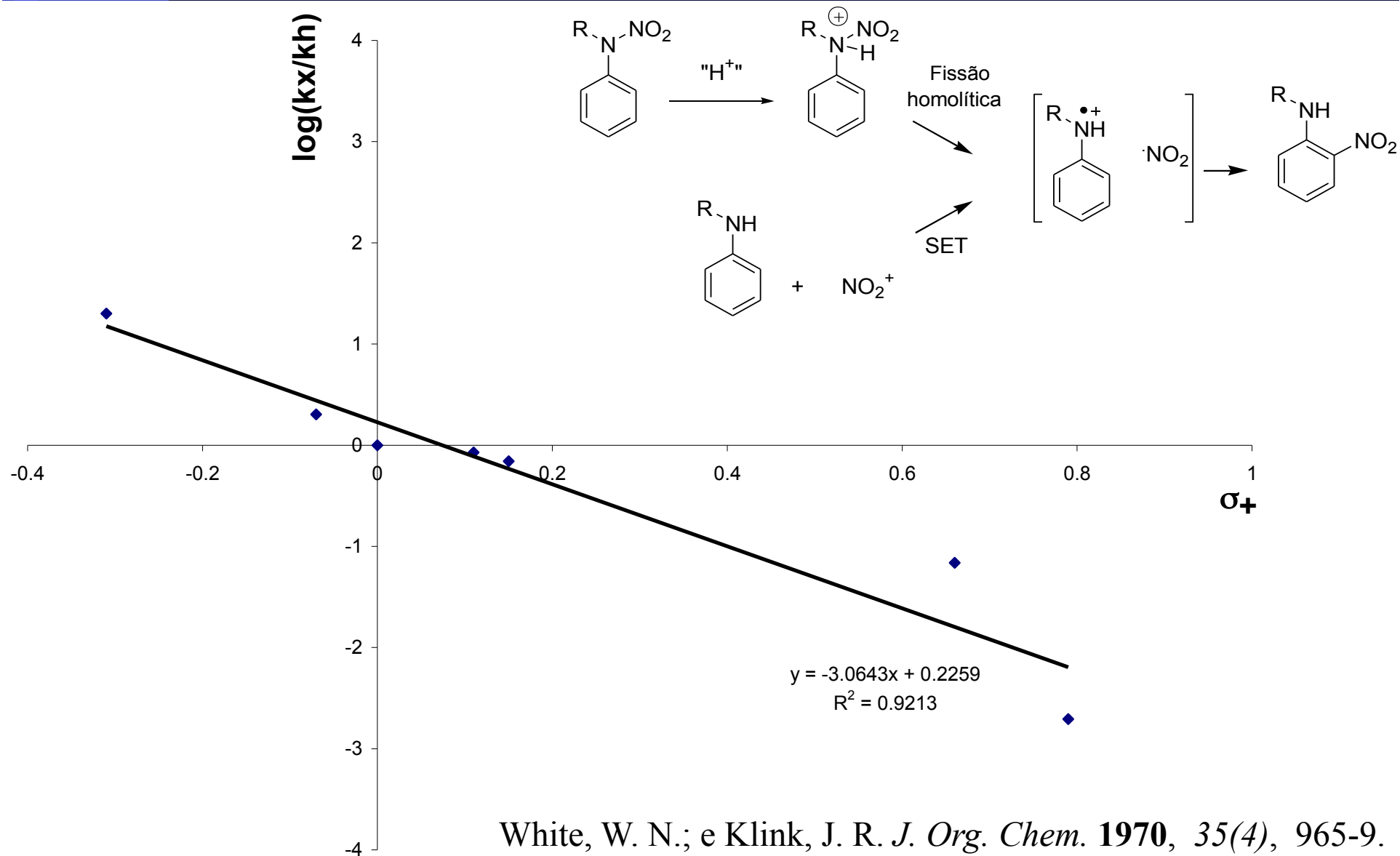
Rearrangement of N-Nitroanilines



SET in aniline nitration?

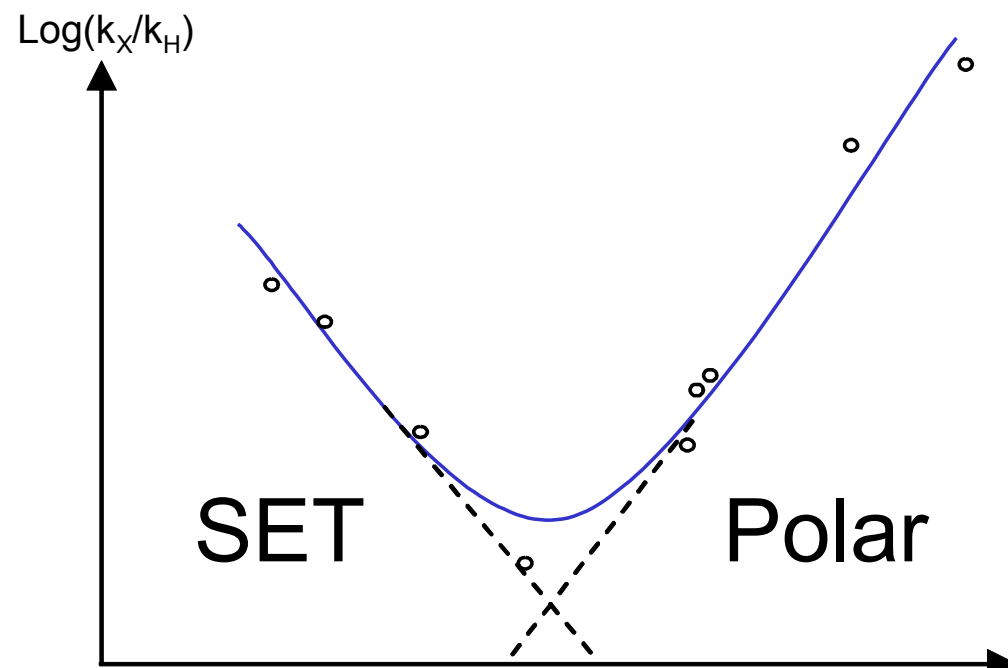
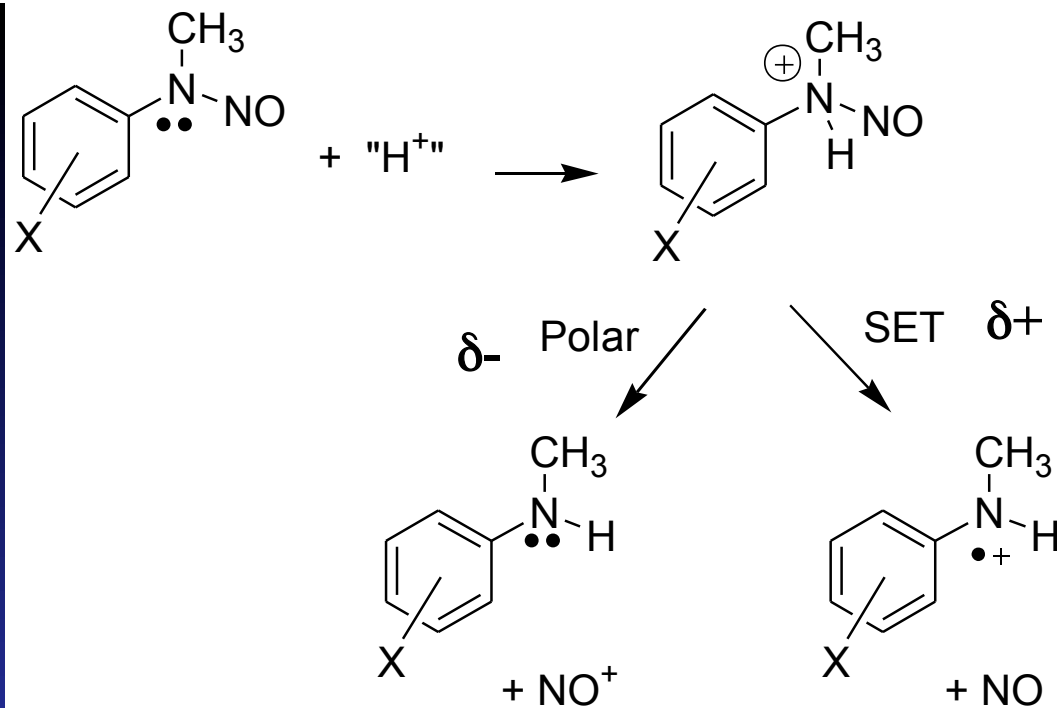
Reação	Energia de Ionização (IE) (eV) ^a	ΔEI para a reação com NO ₂ ⁺ (kcal/mol)
$\text{NO}_2 \rightarrow \text{NO}_2^+ + e$	9.586 ± 0.002	0.00
$\text{PhNH}_2 \rightarrow \text{PhNH}_2^+ + e$	7.72 ± 0.002	-43.0
$\text{p-MeOC}_6\text{H}_4\text{NH}_2 \rightarrow \text{p-MeOC}_6\text{H}_4\text{NH}_2^+ + e$	7.58 ± 0.01	-46.3
$\text{p-MeSC}_6\text{H}_4\text{NH}_2 \rightarrow \text{p-MeSC}_6\text{H}_4\text{NH}_2^+ + e$	7.60 ± 0.01	-45.8
$\text{p-MeC}_6\text{H}_4\text{NH}_2 \rightarrow \text{p-MeC}_6\text{H}_4\text{NH}_2^+ + e$	7.85 ± 0.05	-40.0
$\text{m-MeC}_6\text{H}_4\text{NH}_2 \rightarrow \text{m-MeC}_6\text{H}_4\text{NH}_2^+ + e$	7.50 ± 0.02	-40.7
$\text{p-FC}_6\text{H}_4\text{NH}_2 \rightarrow \text{p-FC}_6\text{H}_4\text{NH}_2^+ + e$	8.18	-32.4
$\text{p-ClC}_6\text{H}_4\text{NH}_2 \rightarrow \text{p-ClC}_6\text{H}_4\text{NH}_2^+ + e$	7.8	-41.2
$\text{m-FC}_6\text{H}_4\text{NH}_2 \rightarrow \text{m-FC}_6\text{H}_4\text{NH}_2^+ + e$	8.33	-29.0
$\text{m-ClC}_6\text{H}_4\text{NH}_2 \rightarrow \text{m-ClC}_6\text{H}_4\text{NH}_2^+ + e$	8.1 ± 0.1	-34.3
$\text{m-BrC}_6\text{H}_4\text{NH}_2 \rightarrow \text{m-BrC}_6\text{H}_4\text{NH}_2^+ + e$	7.7 ± 0.1	-43.5
$\text{p-NCC}_6\text{H}_4\text{NH}_2 \rightarrow \text{p-NCC}_6\text{H}_4\text{NH}_2^+ + e$	8.64 ± 0.04	-21.8
$\text{p-O}_2\text{NC}_6\text{H}_4\text{NH}_2 \rightarrow \text{p-O}_2\text{NC}_6\text{H}_4\text{NH}_2^+ + e$	8.34 ± 0.01	-28.7

Hammett correlation



White, W. N.; e Klink, J. R. *J. Org. Chem.* **1970**, *35(4)*, 965-9.

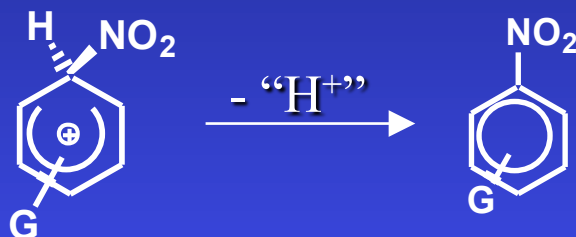
Rearrangement of N-Nitrosoanilines



Mechanistic Proposal



Unoriented
electrostatic complex



Rate controlling step: Depends on the ionization potential of ArH

Conclusions: Nitration

- Reaction of NO_2^+ with $\text{ArH} \rightarrow \text{SET}$
- Solvation makes
 - **Deactivated aromatics** \rightarrow Adducts formed
 - **Activated aromatics** \rightarrow SET is favored
- SET mechanism is surely involved in nitration of activated aromatics
- Mechanistic continuum between polar mechanism (Ingold-Hughes) and SET: Depends on ArH and on solvation
- The higher the HOMO of ArH , lower the “barrier” for the SET and aromatic is more easily undergo oxidation.

Nitration: Mechanistic Continuum

Polar Mechanism (Ingold-Hughes)

- Substrates with high PI (meta directing substituents)
- Non oxidant electrophiles
- Solvents with high ϵ (H_2SO_4 , polar protic solvents, etc)



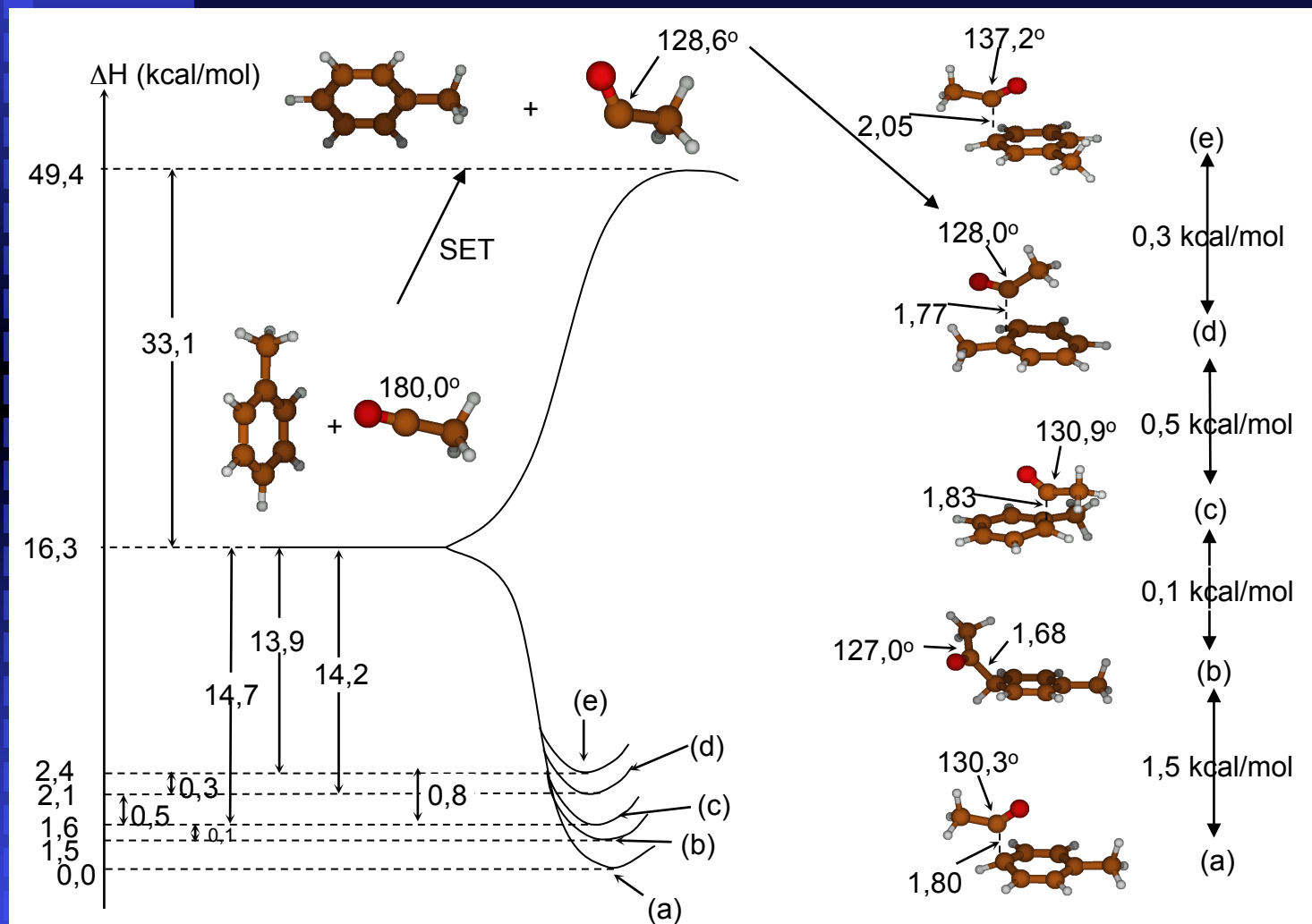
SET Mechanism

- Substrates with low PI (ortho-para directing substituents)
- Oxidant electrophiles
- Solvents with low ϵ (aprotic polar solvents, SO_2 , CH_2Cl_2 , etc)

Other Typical Electrophilic Aromatic Substitution

- Friedel-Crafts Alkylation
- Friedel-Crafts Acylation
- Halogenation
- Sulfonation
- Nitrosation
- Metalation

Acetilação do tolueno



Eletrófilo X Oxidante ←

Ativação pelo CH₃



Permite a formação de um complexo σ em para, porém menos estável que o complexo π correspondente.

Complexo σ em orto não foi encontrado.



Pequenas diferenças de Energia X efeito estérico?

Parâmetros geométricos

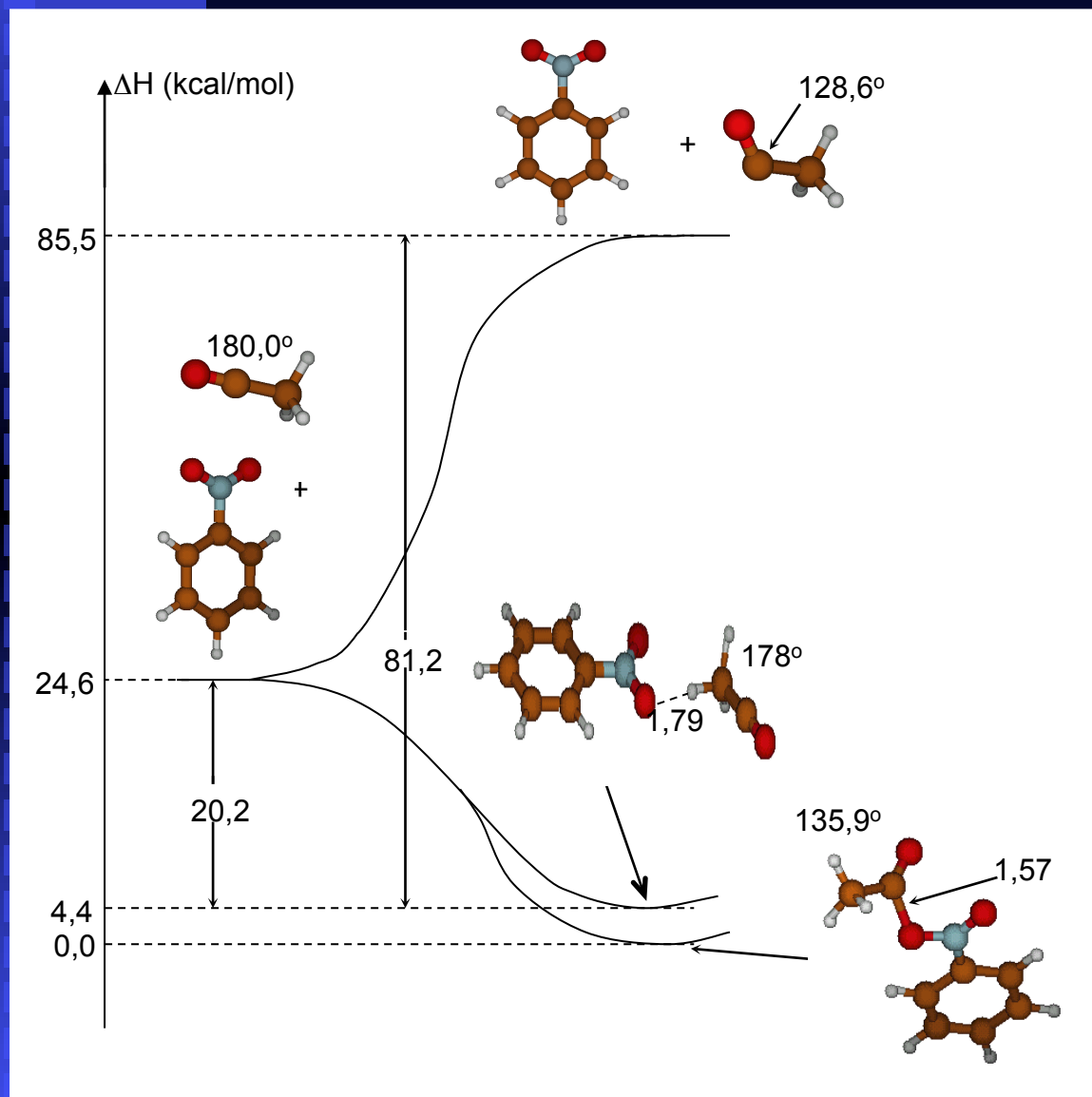


Ângulo do grupo acílio nos complexos é muito semelhante ao do radical acila



Complexo π X complexo SET

Acetilação do nitrobenzeno



Desativação pelo grupo nitro



Processo SET muito desfavorecido



Complexos π não foram encontrados

Dois mínimos encontrados:
ambos de interação do íon
acetílio com a base n do grupo
nitro (átomo de oxigênio), mais
forte do que a base π do anel.

Kinetic Isotope Effect for Propionylation and Benzoylation of Aromatics

$\text{CH}_3\text{CH}_2\text{CO}^+\text{SbF}_6^-$
Toluene-benzene- d_6 $k_{\text{H}}:k_{\text{D}} = 2.84$
Benzeno- d_6

Toluene-benzene- d_6 $k_{\text{H}}:k_{\text{D}} = 3.06$
Tolueno- d_5 -benzeno
Toluene- d_5

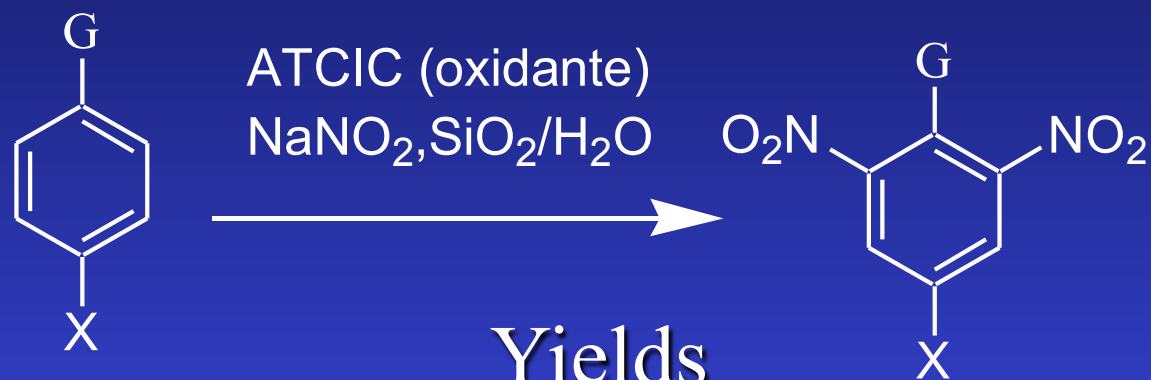
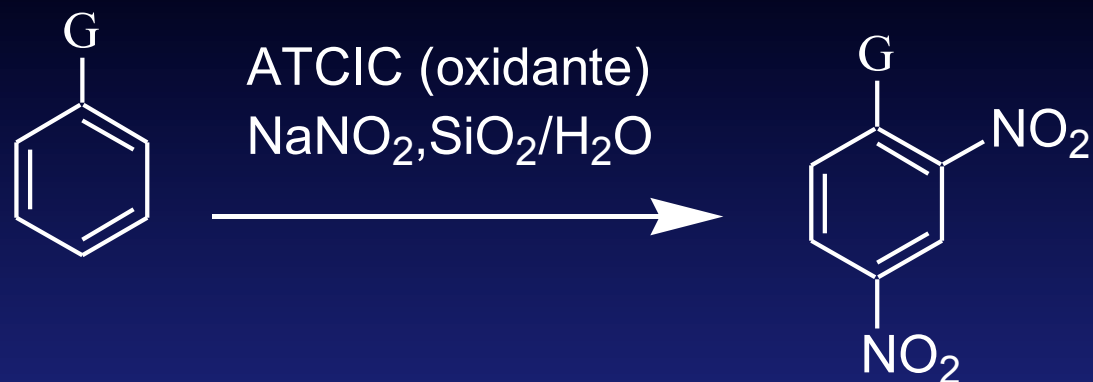
$\text{C}_6\text{H}_5\text{CO}^+\text{SbF}_6^-$
p-Xilene-benzene $k_{\text{H}}:k_{\text{D}} = 1.80$
Benzene- d_5

p-Xileno-benzeno- d_6
Toluene- d_5 -benzene $k_{\text{H}}:k_{\text{D}} = 1.65$
Toluene- d_5 -benzene
Toluene- d_5

Other kinetic isotopic effects:

Reaction	Type	k_H/k_D
$\text{PhNMe}_2 + \text{Br}_2$	Halogenation	2.6
$\text{PhOMe} + \text{ICl}$	Halogenation	3.8
$\text{PhBr} + \text{H}_2\text{SO}_4$ (oleum)	Sulfonation	1.5
$\text{PhOH} + \text{NO}^+$	Nitrosation	4.1
$\text{PhH} + \text{Hg}(\text{OAc})_2$	Metalation	6.0

New Reactions: New paradigms



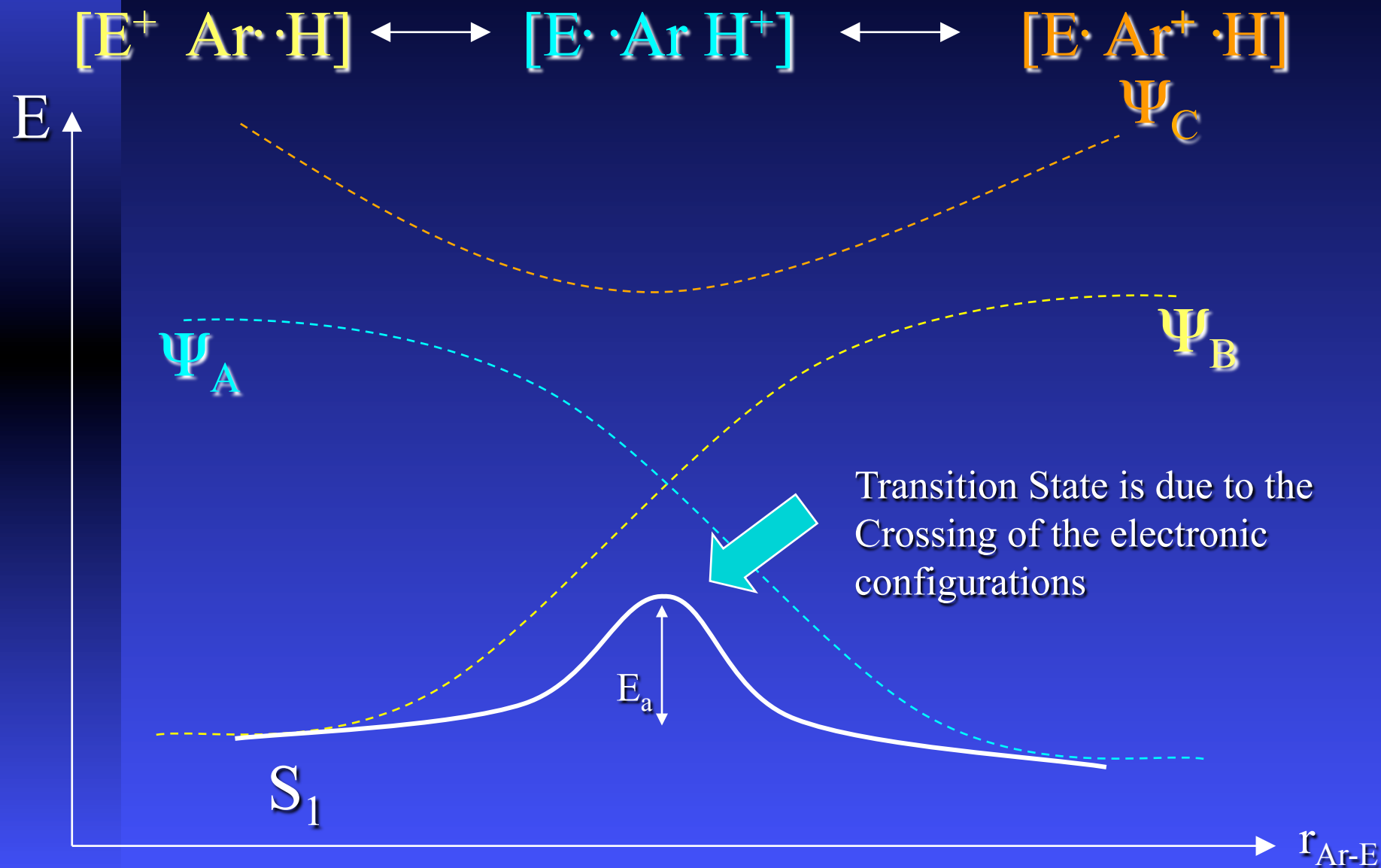
Yields

G = OH, X = H	98%
G = OH, X = F	99%
G = OH, X = CN,	95%
G = OH, X = NHAc	33%

Zolfigol, Madrakian e Ghaemi
Synlett, 2003, 14, 2222-2224

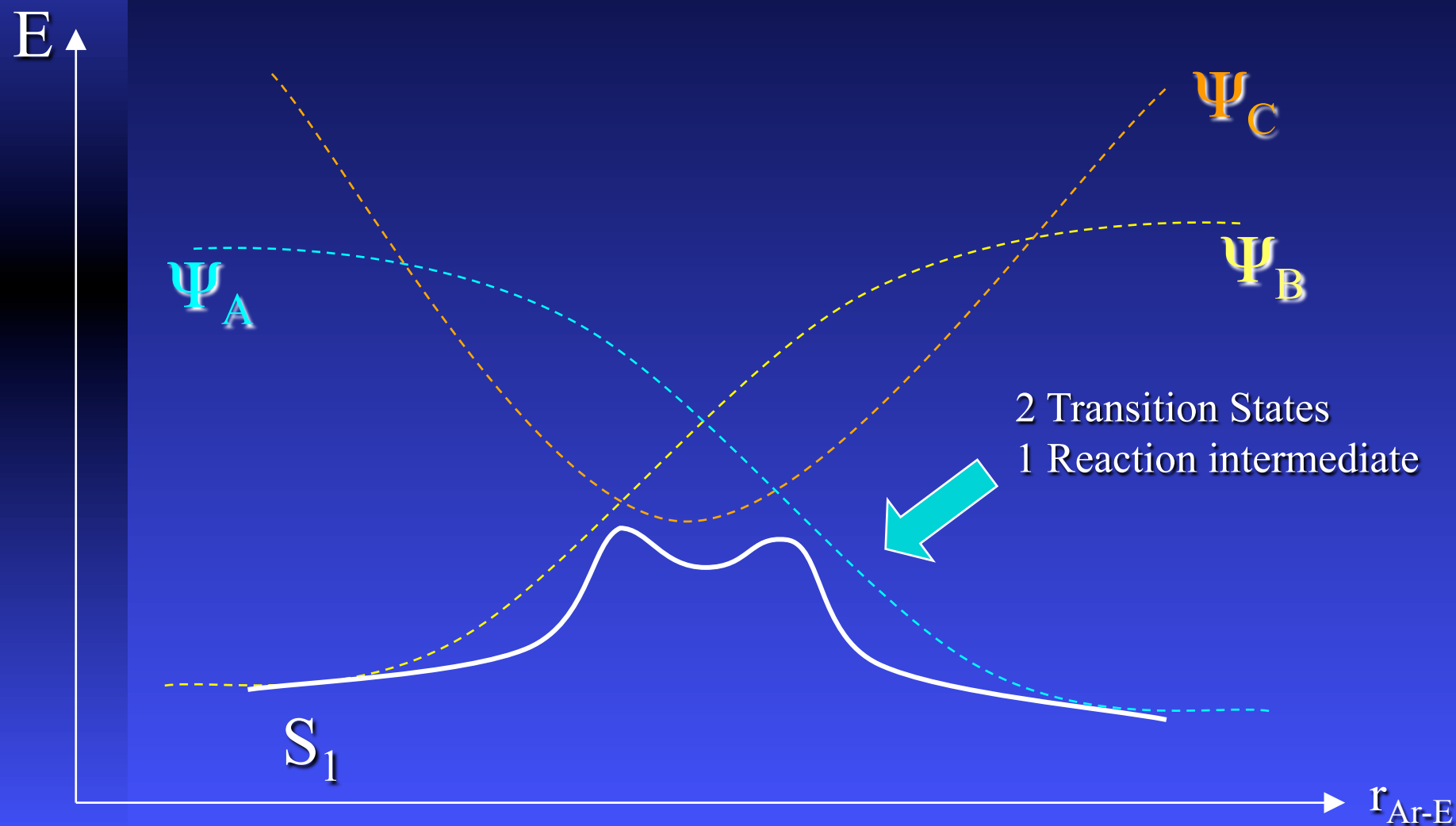
Reaction Profiles: States and Electronic Configurations

Case 1: Ψ_c of high energy



Reaction Profiles: States and Electronic Configurations

Case 2: Ψ_c of low energy



Conclusion

- The electrophilic aromatic substitution mechanism can be a spectrum of possibilities between the SET or Polar (Ingold-Hughes) mechanism, depending on the oxidative character of the electrophile and the ionization potential of the aromatic substrate.
- Solvent/medium effects can influence the reactional pathway

Perspectives

- Reinvestigation of other electrophilic aromatic and aliphatic substitution under the SET paradigm
- Electrophiles, Superelectrophiles or Superoxidants?
- The single electron transfer process and theories of reactivity
- Development of new reaction under the new paradigm.

Team

▪ Coworkers

- José Walkimar de M. Carneiro (IQ/UFF)
- Marcos N. Eberlin (IQ/UNICAMP)
- Regina Sparapan (IQ/UNICAMP)
- Adão A. Sabino (IQ/UNICAMP)
- Liliane (IQ/UNICAMP)
- Márcio Contrucci de Mattos (IQ/UFRJ)

▪ Students

- Fabio Luis Rodrigues (IC/UFRJ)
- Leonardo Almeida (PG/DQO/UFRJ)
- Gabriela Fonseca (PG/DQO/UFRJ)
- Felipe Fleming Pereira (PG/DQO/UFRJ)
- Jorge Freitas (IQ/UFF)

▪ Students (Cont.)

- Rachel Moraes (IC/UFRJ)
- Leandro (IC/UFRJ)
- Ana Cristina Paes Leme (IC/UFRJ)
- Vivian Mazzei (IC/UFRJ)
- Thiago Muza (IC/UFRJ)
- Rejane Magalhães Ramos (IC/UFRJ)
- Carolina Leite Araujo (IC/UFRJ)



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Instituto de Química

Universidade Federal do Rio de Janeiro



Prof. Pierre M. Esteves

(pesteves@iq.ufrj.br)

www.iq.ufrj.br/~pesteves

