KINETIC DATA ANALYSIS AND GRAPHING

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Overview

- Chemical Kinetics
- Chemical Kinetics Procedures
- Nucleophilic Aromatic Substitution Reactions
- Some Challenges
- A case for Open Science in Africa.

Chemical Kinetics

- The area of chemistry that is concerned with the speeds, or rates, of reactions is called **chemical kinetics.** Chemical kinetics involves the study of the rates and mechanisms of chemical reactions.
- Chemical kinetics is a subject of broad importance.
- It relates, for example, to how quickly a medicine is able to work, to whether the formation and depletion of ozone in the upper atmosphere are in balance, and to industrial problems such as the development of catalysts to synthesize new materials.

The Objects of Chemical Kinetics

There are broadly two separate, although, related objects of chemical kinetics; rates and mechanisms.

- The analysis of the mechanisms by which reactions occur i.e. the sequence of elementary steps giving rise to the overall reaction.
- The determination of the absolute rates of the reaction of its individual steps.

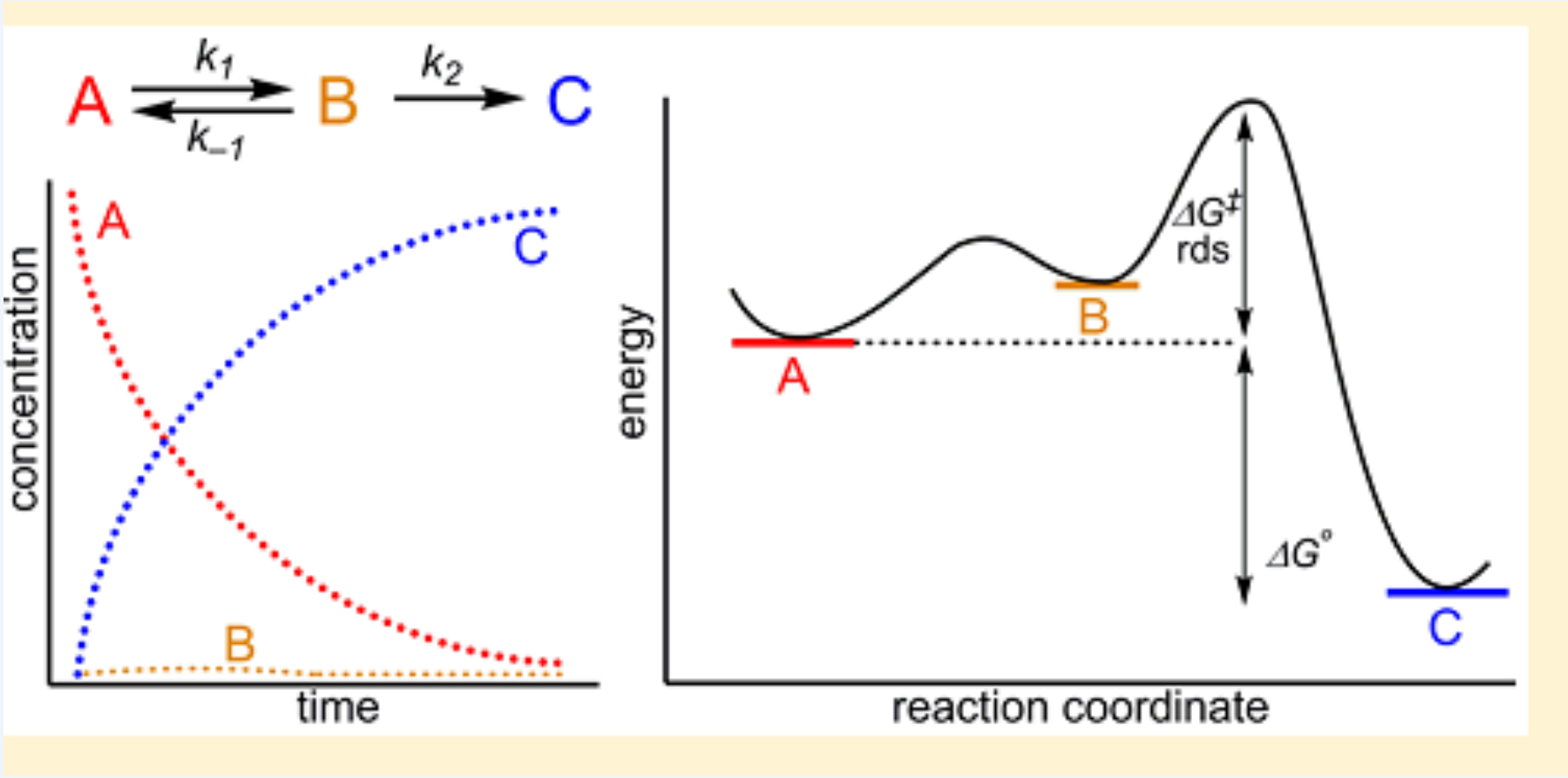
Kinetic studies provide valuable practical information on the rate under experimental conditions such as;

- reactants concentration,
- temperature and
- medium of reaction.

This is then used to provide the basis for determining the mechanism by which a reaction occurs.

Kinetic Procedures

- The starting point of most kinetic investigation of chemical reactions is the determination of the reaction rate and its dependent upon the concentration of the species involved.
- The overall rate of a reaction rate is not normally measured directly; rather, the concentration of the reactant or product is monitored as a function of time.



Mechanistic understanding of chemical reactions drives research and guides teaching of reactivity in chemistry. Upper-level physical organic or organometallic chemistry courses often discuss reaction mechanism in detail, in the context of prototypical example reactions.

Table 1. Differential Equations and Integrated Rate Laws for Use in Graphical Kinetic Analysis

Order	Differential Equation	Integrated Expression	Half-Life Expression	Graph Drawn (Linear Fit)
0	$\frac{-\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = k[\mathrm{A}]^0 = k$	$[\mathrm{A}]_t = [\mathrm{A}]_0 - kt$	$t_{1/2} = \frac{[\mathrm{A}]_0}{2k}$	$[\mathrm{A}]_t$ vs t (slope $= -k$)
1	$\frac{-\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = k[\mathrm{A}]$	$\ln[\mathrm{A}]_t = \ln[\mathrm{A}]_0 - kt$	$t_{1/2} = \frac{\ln 2}{k}$	$\ln[\mathrm{A}]_t$ vs t (slope $= -k$)
2	$\frac{-\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = k[\mathrm{A}]^2$	$\frac{1}{[\mathrm{A}]_t} = \frac{1}{[\mathrm{A}]_0} + kt$	$t_{1/2} = \frac{1}{k[\mathrm{A}]_0}$	$\frac{1}{[\mathrm{A}]_t}$ vs t (slope $= +k$)
1/2	$\frac{-\mathrm{d}[\mathrm{A}]}{\mathrm{d}t} = k[\mathrm{A}]^{1/2}$	$[\mathrm{A}]_t^{1/2} = [\mathrm{A}]_0^{1/2} - \frac{1}{2}kt$	$t_{1/2} = \frac{(2-\sqrt{2})[\mathrm{A}]_0^{1/2}}{k}$	$[\mathrm{A}]_t^{1/2}$ vs t $\left(\text{slope} = -\frac{1}{2}k\right)$

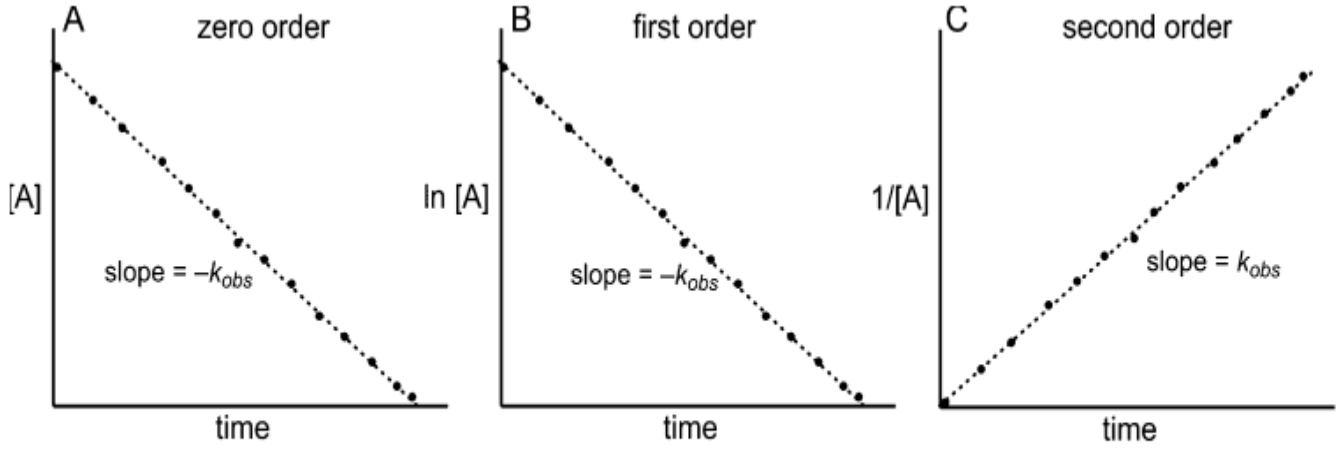


Figure 1. Graphical analysis methods illustrating the expected linear fit for zero-order (A), first-order (B), and second-order (C) reactions. Reaction data can be plotted each way to determine which order provides the most accurate linear fit.

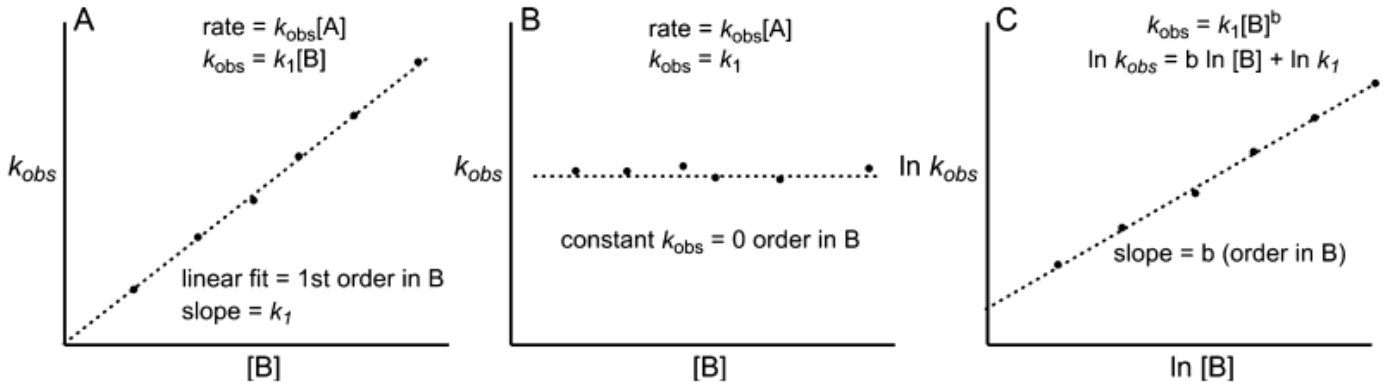


Figure 2. Graphical analysis for determination of order in [B] and rate constant k_1. A linear dependence is observed if the reaction is first order in [B] (A) while no dependence is observed if the reaction is zero order in [B] (B). A logarithmic treatment (C) should result in a linear correlation in which the slope reveals the order in [B]. In all cases, [A] is held constant and 10-fold less than [B].

Kinetic Analysis of Complex Systems.

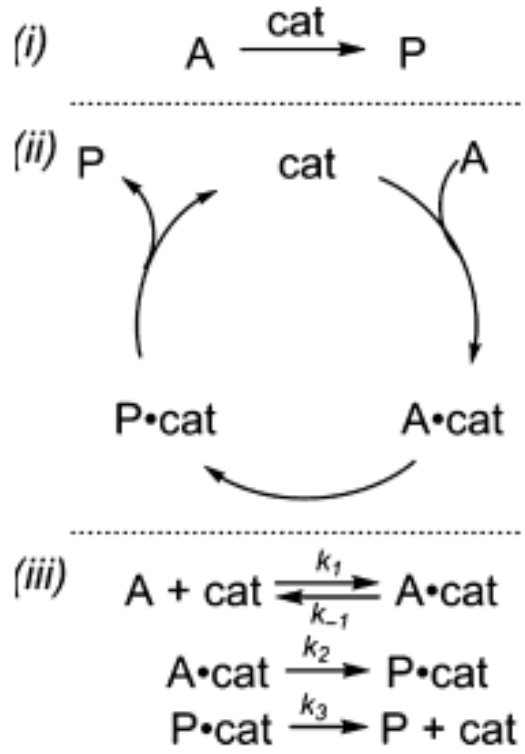


Figure 3. Different schematic representations of a catalytic reaction.

Enzyme Kinetics

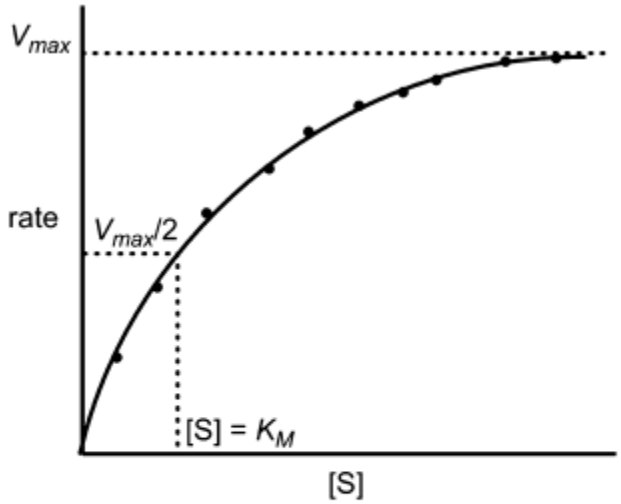
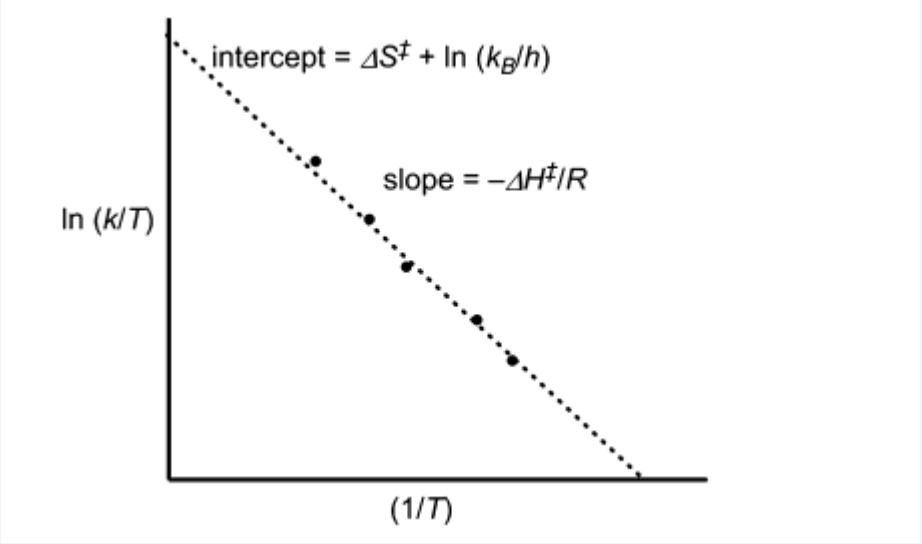
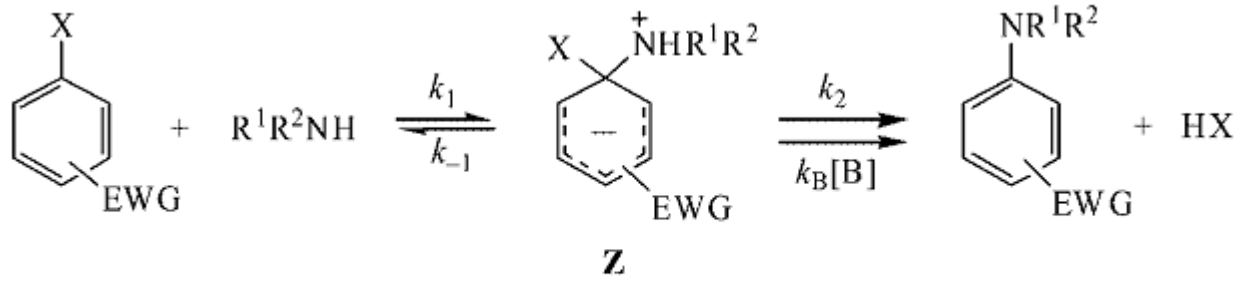


Figure 4. Plot of rate vs substrate concentration, [S], used in Michaelis–Menten and reaction progress kinetic analysis.

Transition-State Theory and Temperature Dependence.



Nucleophilic Aromatic Substitution



EWG = electron withdrawing groups

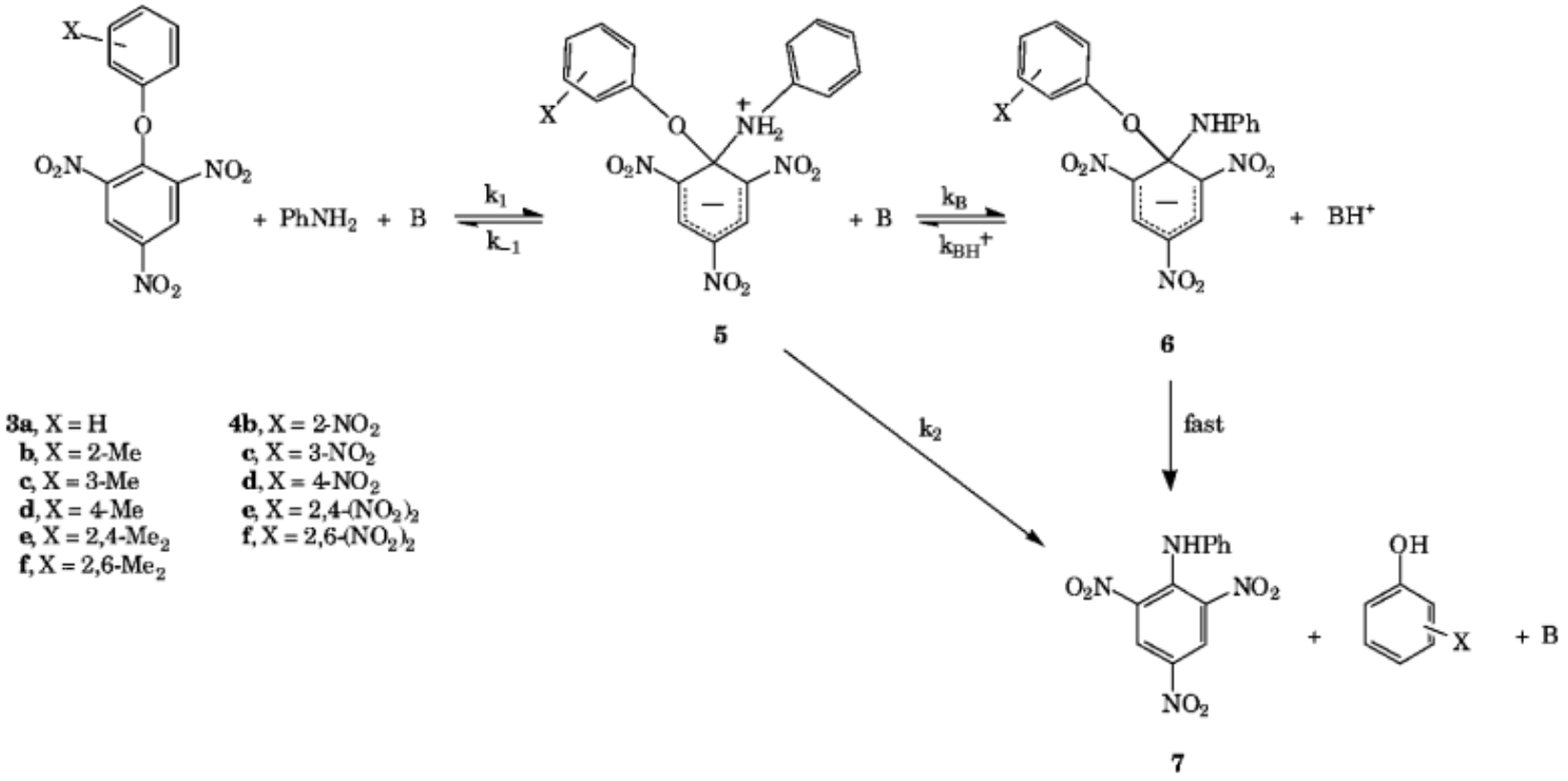
1.Nucleofugality
2.Nature of nucleophile
3.Stereoelectronic effects
4. Solvent effects.
5. Base catalysis

Nucleophilic Aromatic Substitution (S_NAr) Reactions

- Of the 1086 unique small molecules approved by the U.S.Food and Drug Administration (FDA), 640 are found in their assemblage, where at least one nucleophilic aromatic substitution reaction (S_NAr) is involved.
- S_NAr reaction is used once or more in synthetic schemes en route to the following best-selling FDA-approved small molecules: abacavir, imiquimod, erlotinib, levofloxacin, moxifloxacin, pioglitazone, rosiglitazone, pazopanib, febuxostat, itraconazole, ziprasidone, olanzapine, and timolol.
- A number of these drugs are listed on the World Health Organization's List of Essential Medicines.
- S_NAr reaction is an important reaction within industrial circles.

Isley N. A *et al*, Org. Lett., 2015, 17, 4734-4737

Leaving group effects on the Mechanism of S_NAr Reactions



Scheme 2

J. Phys. Org. Chem 2004, 17, 65-70

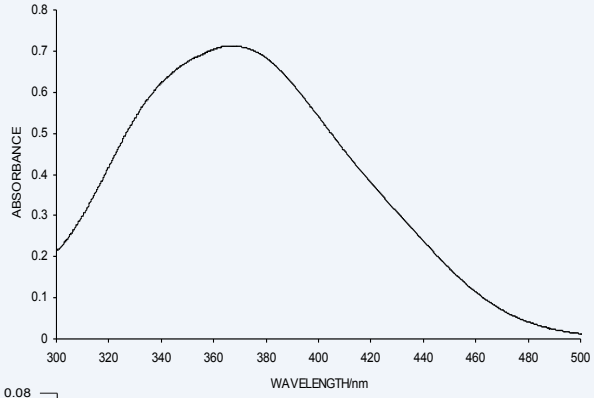
Data Analysis

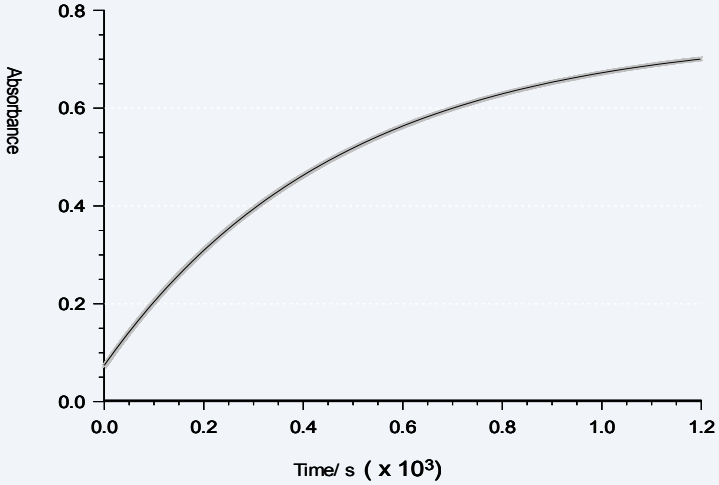
- Quantitative data for individual rate coefficients was obtained by a combination of kinetics data software, and spectrophotometry.
- This involves following a time dependent change in a chemical reactions.
- Spreadsheet program can then be used to analysed the data for parameters of interest. Examples of such spreadsheet program include;

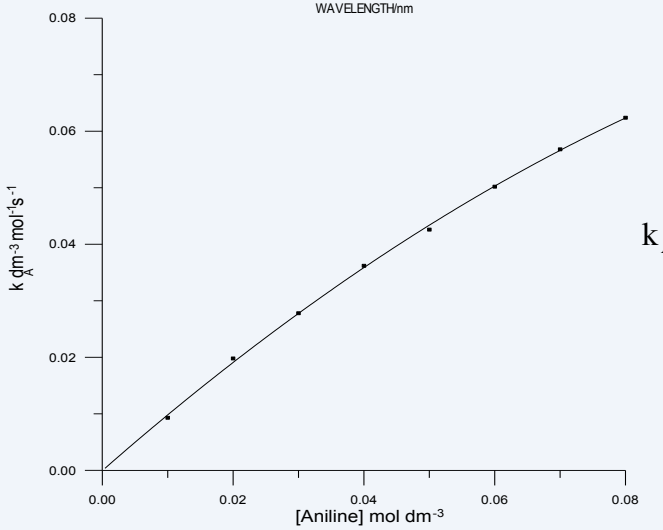
- Macromath Scientist
- OriginPro
- Sigmaplot
- SimFit

(a) UV-Vis Spectrum of 5×10^{-5} mol dm^{-3} 2,4,6-trinitrodiphenylamine

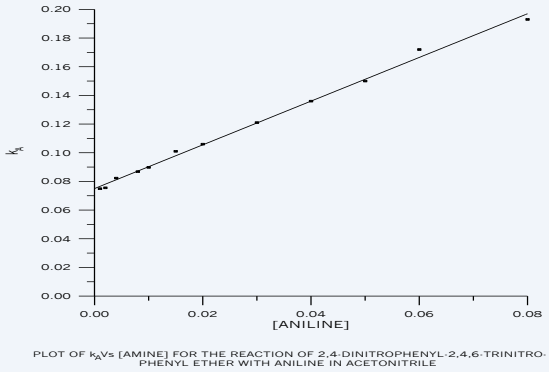
(b) Kinetic traces involving 5.0×10^{-5} mol dm^{-3} of **3.1** and 0.01 mol dm^{-3} aniline in acetonitrile, λ = 365nm at 25^0C







$$k_A = \frac{K_1 k_2 + K_1 k_{An}[An]}{1 + \frac{k_2}{k_{-1}} + \frac{k_{An}[An]}{k_{-1}}}$$



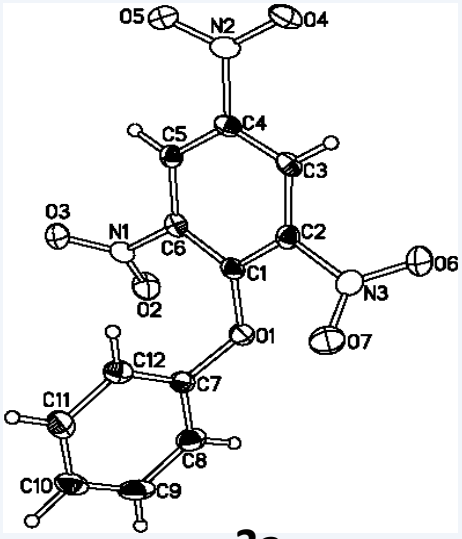
PLOT OF k_AVs [AMINE] FOR THE REACTION OF 2,4-DINITROPHENYL-2,4,6-TRINITRO-PHENYL ETHER WITH ANILINE IN ACETONITRILE

Table 3. Summary of the rate data for the reactions of **3** and **4**, X-phenyl-2,4,6-trinitrophenyl ethers, with aniline in acetonitrile

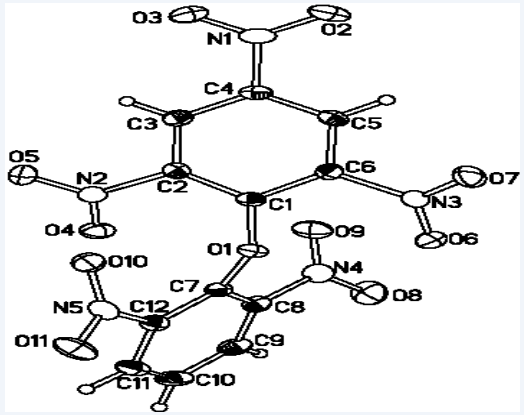
Reactant	X	K_1k_{An} ($dm^6\ mol^{-2}\ s^{-1}$)	k_{An}/k_{-1} ($dm^3\ mol^{-1}$)	k_1 ($dm^3\ mol^{-1}\ s^{-1}$)	K_1k_{DABCO} ($dm^6\ mol^{-2}\ s^{-1}$)	k_{An}/k_{DABCO}	K_1k_2 ($dm^3\ mol^{-1}\ s^{-1}$)
3f	2,6-$(CH_3)_2$	0.0011 ± 0.0001	<0.2	>0.0055	—	—	—
3e	2,4-$(CH_3)_2$	0.10 ± 0.005	<1	>0.1	—	—	—
3b	2-CH_3	0.15 ± 0.01	1 ± 0.5	0.13 ± 0.05	—	—	—
3c	3-CH_3	0.34 ± 0.02	2.6 ± 1	0.13 ± 0.05	—	—	—
3d	4-(CH_3)	0.48 ± 0.02	1 ± 0.5	0.48 ± 0.20	1.5 ± 0.3	0.32 ± 0.10	—
3a	4-H	0.48 ± 0.02	2 ± 1	0.24 ± 0.10	1.6 ± 0.2	0.30 ± 0.05	—
4b	2-NO_2	0.95 ± 0.03	3 ± 1	0.32 ± 0.10	—	—	—
4c	3-NO_2	1.13 ± 0.05	3 ± 1	0.38 ± 0.10	3.2 ± 0.4	0.35 ± 0.10	—
4d	4-NO_2	1.03 ± 0.03	4 ± 1	0.26 ± 0.08	3.4 ± 0.3	0.30 ± 0.05	—
4e	2,4-$(NO_2)_2$	2.2 ± 0.20	2.7 ± 0.5	0.8 ± 0.3	4 ± 0.5	0.50 ± 0.1	0.08 ± 0.01
4f	2,6-$(NO_2)_2$	—	—	1.5 ± 0.2	—	—	Large

Table 4 Summary of the rate data for the reaction of **4**, Y-phenyl-2,4,6 trinitrophenyl ethers, with aniline in acetonitrile

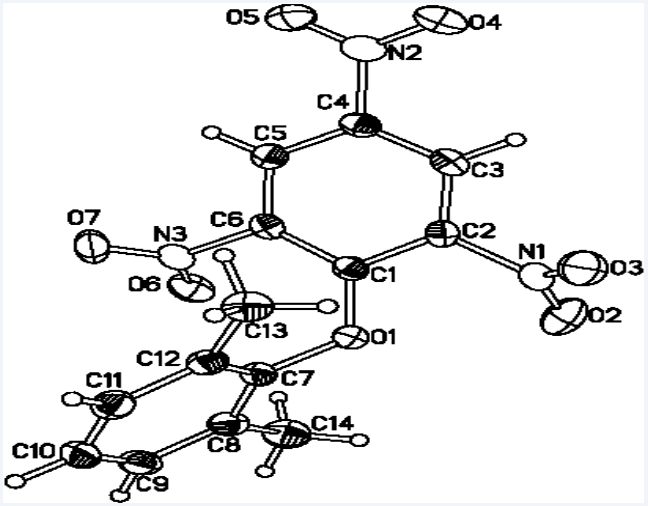
Reactant Y	K_1k_{An}/$dm^6\ mol^{-2}\ s^{-1}$	k_{An}/k_{-1} $dm^3\ mol^{-1}$	k_1/$dm^3\ mol^{-1}\ s^{-1}$	K_1k_{DABCO}/$dm^6\ mol^{-2}\ s^{-1}$	k_{An}/k_{DABCO}
4-CH_3	0.48 ± 0.02	1 ± 0.5	0.48 ± 0.20	1.5 ± 0.3	0.32 ± 0.10
H	0.48 ± 0.02	2 ± 1	0.24 ± 0.10	1.6 ± 0.2	0.30 ± 0.05
4-Br	0.85 ± 0.03	2.6 ± 1	0.33 ± 0.10	2.1 ± 0.1	0.40 ± 0.05
4-Cl	0.95 ± 0.03	3.7 ± 1	0.26 ± 0.08	2.7 ± 0.4	0.35 ± 0.10
4-NO_2	1.03 ± 0.03	4 ± 1	0.26 ± 0.08	3.4 ± 0.3	0.30 ± 0.05
3-NO_2	1.13 ± 0.05	3 ± 1	0.38 ± 0.10	3.2 ± 0.4	0.35 ± 0.10



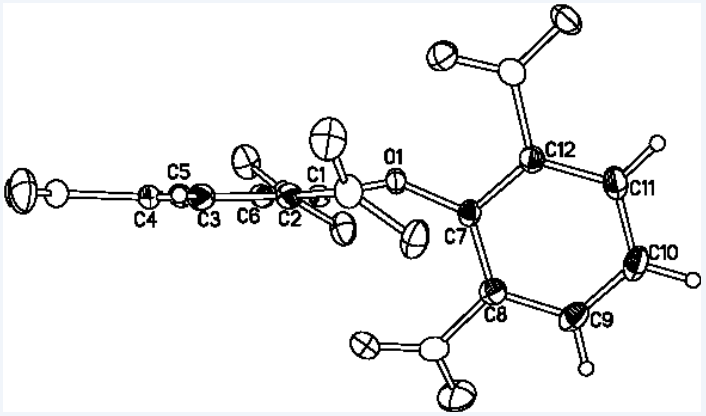
3a



3f



4f



	3a	3f	4f
O(1)—C(1) (Å)	1.350	1.343	1.359
O(1)—C(7) (Å)	1.406	1.423	1.373
C(1)—O(1)—C(7) (°)	120.3	119.4	130.4
2-Nitro (twist) (°)	45	53	45
6-Nitro (twist) (°)	46	58	36
4-Nitro (twist) (°)	14	10	2
Deviation of O(1) from trinitro ring plane (°)	7	6	12
Angle between aromatic rings (°)	66	74	76

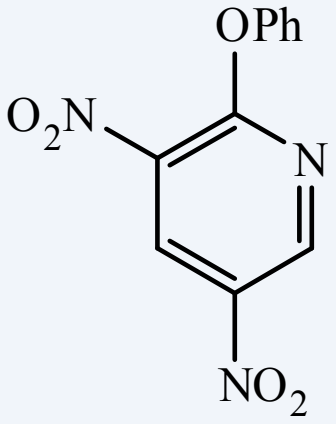
Figure 1. X-ray structures: (a) **3f** and (b) and (c) two perspectives of **4f**

Table 5. Summary of rate data for the reaction of **4d** with ring-substituted anilines **2, a-l** in acetonitrile at 25°C.

Substituent(s), R	K_1k_2 ($dm^3\ mol^{-1}\ s^{-1}$)	K_1k_{An} ($dm^6\ mol^{-2}\ s^{-1}$)	k_{An}/k_{-1} ($dm^3\ mol^{-1}$)	k_1 ($dm^3\ mol^{-1}\ s^{-1}$)	k_{An}/k_2 ($dm^3\ mol^{-1}$)
a, 4–OMe	2.9 ± 0.3	90 ± 10	5 ± 1	18 ± 5	31
b, 4–Me	0.68 ± 0.05	16 ± 1	3.5 ± 1	4.5 ± 1.5	24
c, 3-Me	0.18 ± 0.05	4 ± 0.5	2.5 ± 1	1.6 ± 0.5	22
d, H[a]	0.08 ± 0.01	2.2 ± 0.2	2.7 ± 0.5	0.8 ± 0.3	28
e, 4–F	0.045 ± 0.01	1.25 ± 0.1	2.5 ± 0.5	0.5 ± 0.2	28
f, 4–Cl	$(5 \pm 1) \times 10^{-3}$	0.23 ± 0.02	1.8 ± 0.5	0.12 ± 0.06	46
g, 3–Cl	$(8 \pm 1) \times 10^{-4}$	0.026 ± 0.004	1 ± 0.5	0.026 ± .01	33
h, 2,4–Me_2	0.024 ± 0.004	0.2 ± 0.05	<1		8
i, 2–Me	$(4.5 \pm 0.5) \times 10^{-3}$	0.04 ± 0.005	<1		9
j, 2–Et	$(1.8 \pm 0.4) \times 10^{-3}$	0.011 ± 0.003	<1		6
k, 2–F	$(1 \pm 0.2) \times 10^{-4}$	$(8 \pm 1) \times 10^{-3}$	<1		80
l, 2,6–Me_2	$(6 \pm 1) \times 10^{-5}$				

J. Phys. Org. Chem. 2006; **19:** 75–80

Nucleophilic Heteroaromatic Substitution



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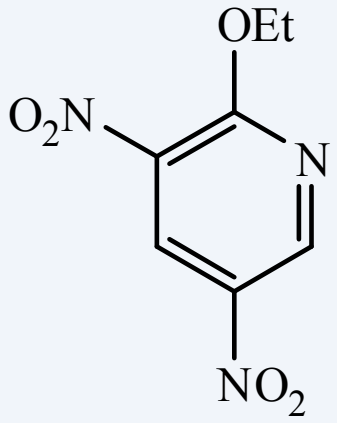
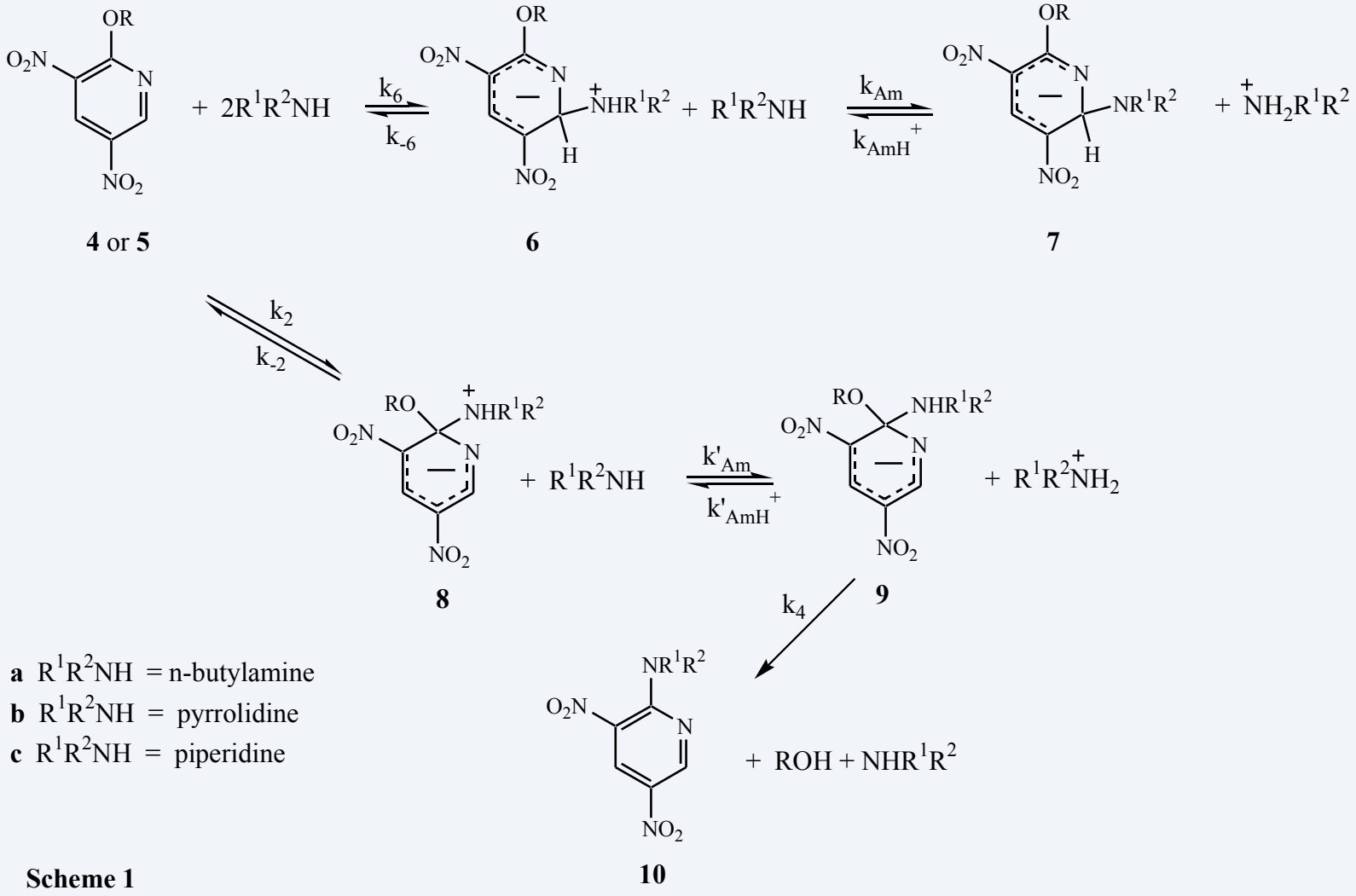


5

Kinetic and equilibrium studies of σ-adduct formation



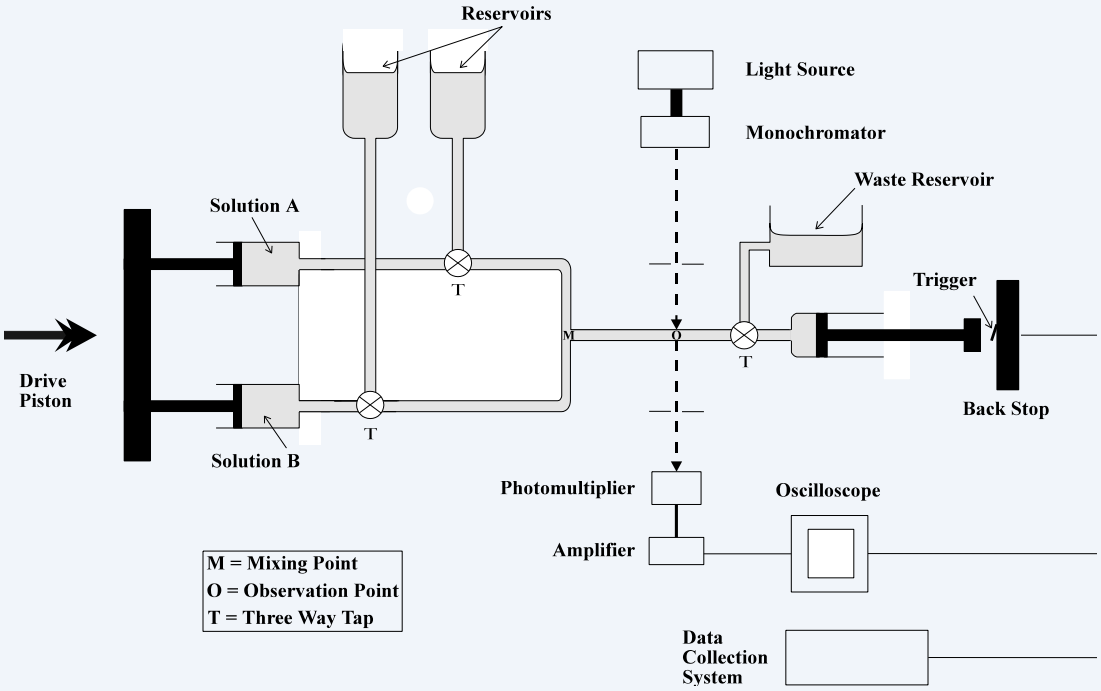
Scheme 1

Kinetic Equation

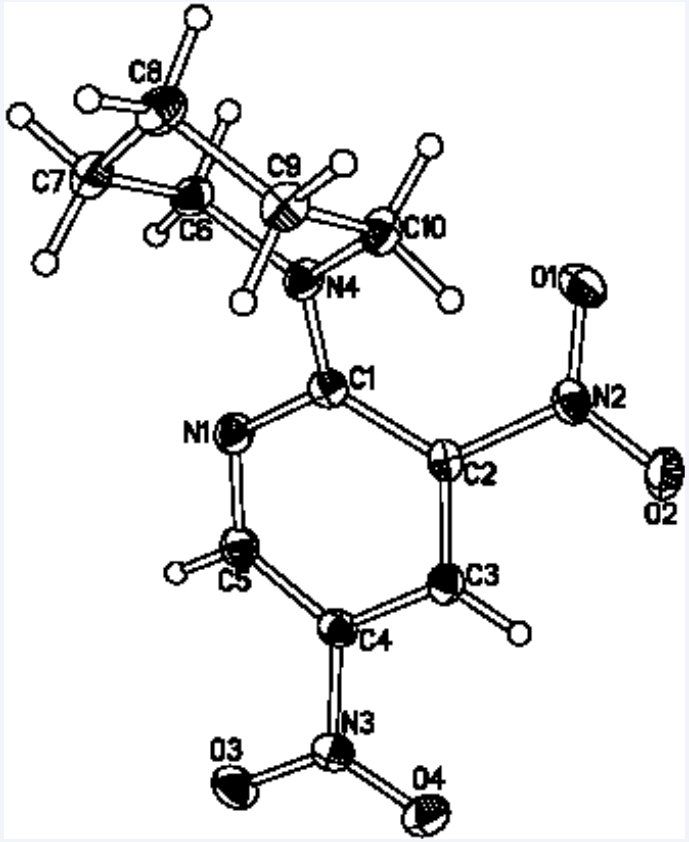
$$k_{fast} = \frac{k_6 k_{Am} [Am]^2}{k_{-6} + k_{Am}[Am]} + \frac{k_{-6}.k_{AmH^+}[AmH^+]}{k_{-6} + k_{Am}[Am]}$$

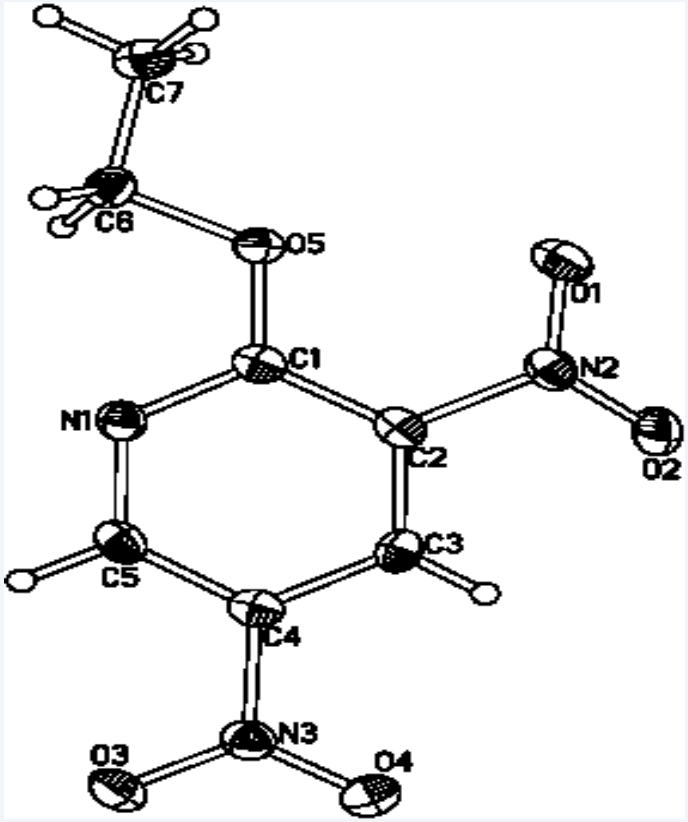
$$k_{slow} = \frac{k_2 k_B [Am]^2}{k_{-2} + k_B[Am]} \cdot \left(\frac{1}{1 + \frac{K_{c,6}[Am]^2}{[AmH^+]}} \right)$$

Applied Photophysics SX-17MV Stopped-flow Spectrometer



X-Ray Crystal Structure Determination





Org. Biomol. Chem., 2003, **1**, 1004–1011

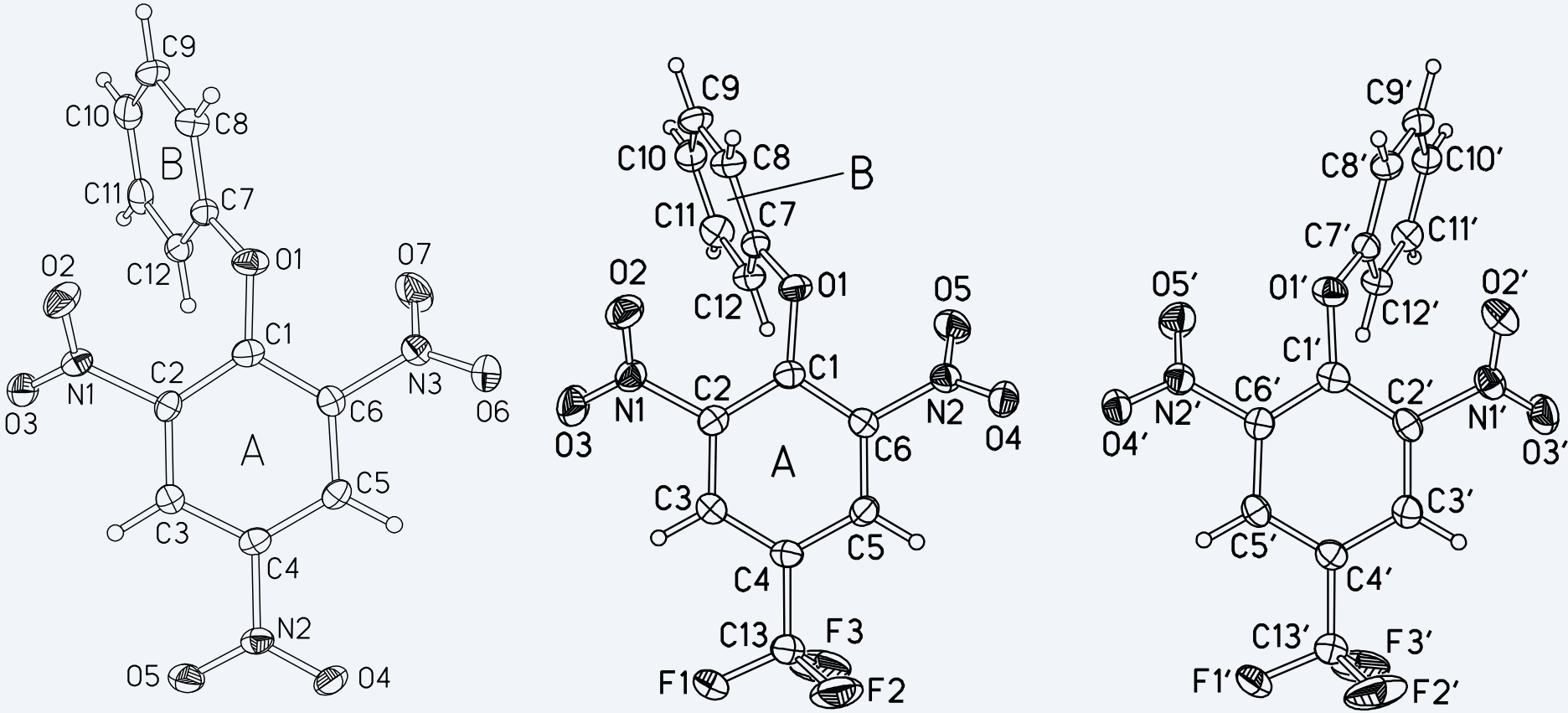
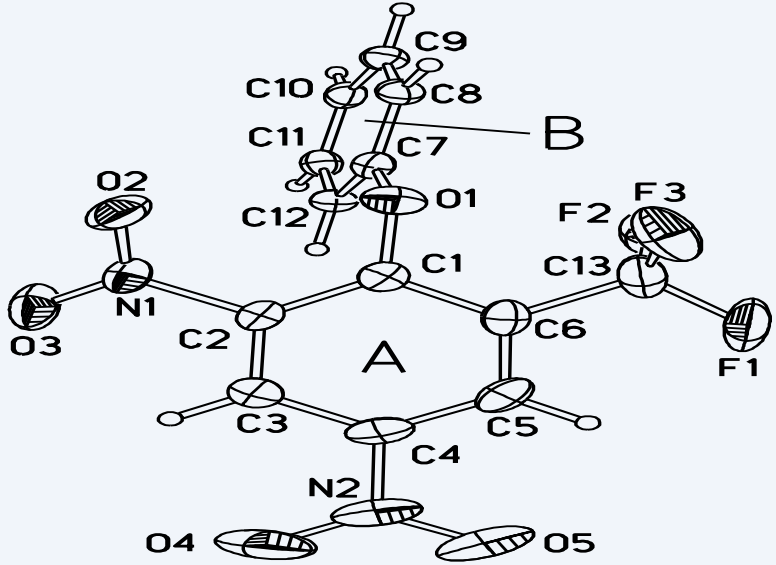
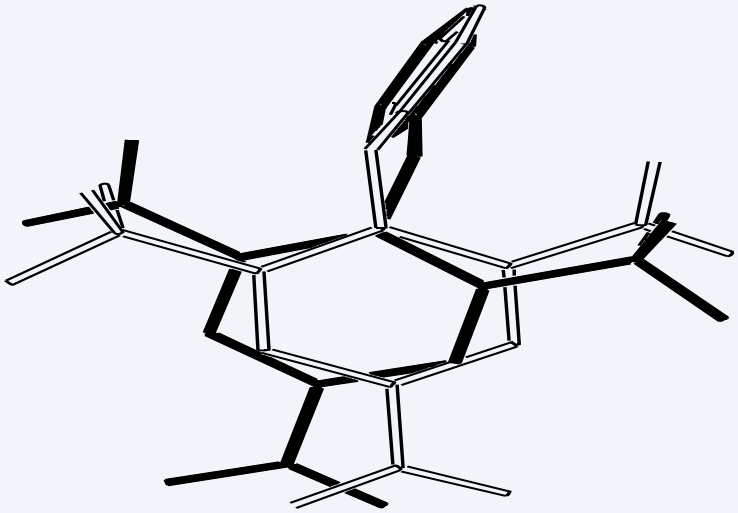


Figure 2. Independent molecules I (left) and II in the structure of **3b**, projected on the plane of ring A. Minor (10%) orientations of the CF_3 groups are not shown.

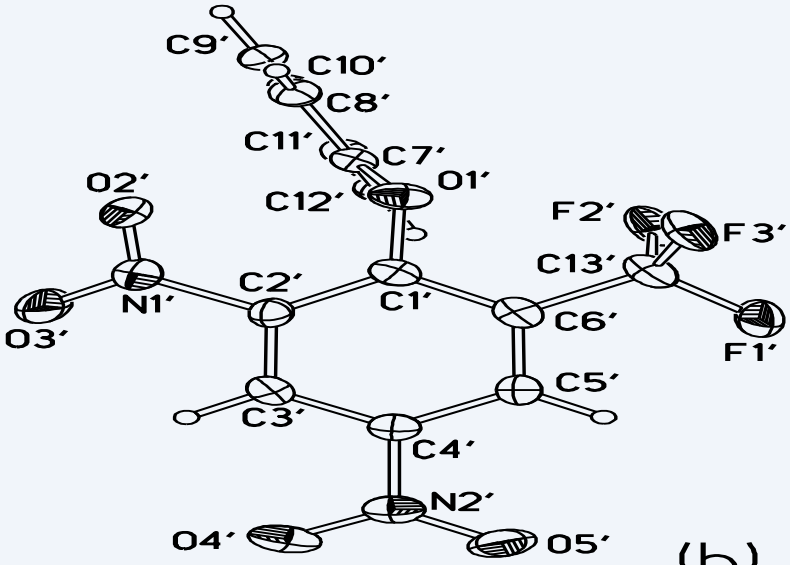
Deposited in the Cambridge Crystallographic Data Centre (CCDC)


C9
C10
C8
C11
C7
B
O2
C12
O1
F3
F2
C1
C13
N1
O3
C2
A
C6
F1
C3
C5
C4
N2
O4
O5

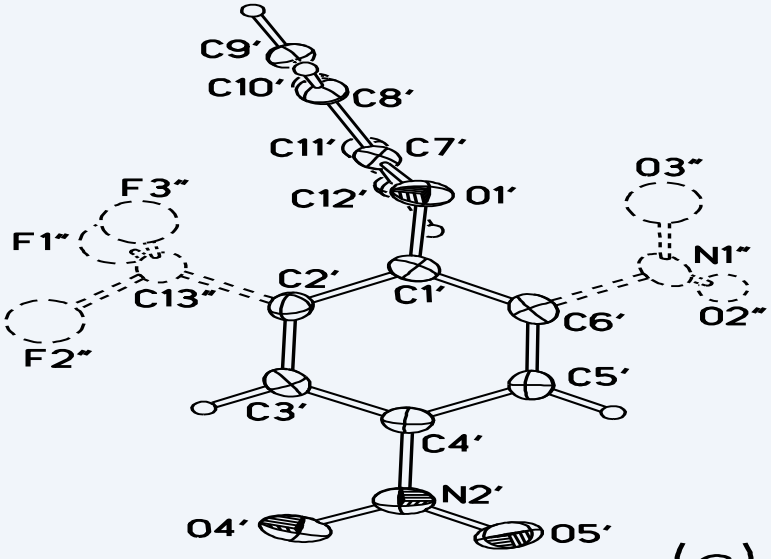
(a)



(d)


C9′
C10′
C8′
C11′
C7′
O2′
O1′
C12′
F2′
F3′
C13′
C2′
N1′
C1′
O3′
C6′
F1′
C5′
C3′
C4′
N2′
O4′
O5′

(b)


C9′
C10′
C8′
C11′
C7′
O3″
F3″
C12′
O1′
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N1″
C13″
C2′
C1′
O2″
C6′
F2″
C5′
C3′
C4′
N2′
O4′
O5′

(c)

DOI: 10.1002/ejoc.200500774

Effects of *ortho*- and *para*-Ring Activation on the Kinetics of S_NAr Reactions of 1-Chloro-2-nitro- and 1-Phenoxy-2-nitrobenzenes with Aliphatic Amines in Acetonitrile

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Keywords: Kinetics / Nucleophilic aromatic substitution / Steric hindrance / Substituent effects

Rate constants are reported for reaction of 4-substituted 1-chloro-2,6-dinitrobenzenes **1**, 6-substituted 1-chloro-2,4-dinitrobenzenes **2**, and some of the corresponding 1-phenoxy derivatives, **3** and **4**, with *n*-butylamine, pyrrolidine and piperidine in acetonitrile as solvent. Values of k_1, the rate constant for nucleophilic attack at the 1-position, increase with increasing ring-activation but may be reduced by steric repulsion at the reaction centre which increases in the order Cl < OPh, and *n*-butylamine < pyrrolidine ≈ piperidine. *ortho*-Substituents may also have adverse steric effects, and those of the trifluoromethyl group are particularly serious. X-ray crystal structures of phenyl 2,4-dinitro-6-trifluoromethylphenyl ether and phenyl 2,6-dinitro-4-trifluoromethylphenyl ether are reported. Base catalysis in the 1-phenoxy derivatives is attributed to rate-limiting proton transfer from the zwitterionic intermediates **6** to base. Values of rate constants for this process decrease with increasing steric congestion at the reaction centre and in the order *n*-butylamine > pyrrolidine > piperidine.

Table 2. Effects of ring-substituents on the relative reactivities, k_1 values, of **1** and **2** with aliphatic amines in acetonitrile at 25 °C.[a]

Substrate, R	*n*-Butylamine	Pyrrolidine	Piperidine
1a, 4-H	1	1	1
1b, 4-CF_3	220	393	470
1c, 4-CO_2Me	273	540	732
1d, 4-CN	$1.7 \cdot 10^3$	$4.2 \cdot 10^3$	$4.6 \cdot 10^3$
1f, 4-NO_2	$5.7 \cdot 10^3$	$1.8 \cdot 10^4$	$2.8 \cdot 10^4$
2a, 6-H	1	1	1
2b, 6-CF_3	56	2.2	1.6
2e, ring N	$3.6 \cdot 10^3$	$4.3 \cdot 10^3$	$3.6 \cdot 10^3$
2f, 6-NO_2	$9.7 \cdot 10^3$	760	$1.2 \cdot 10^3$

[a] For a given amine values are compared to the reactivity with **1a**, and **2a**, respectively.

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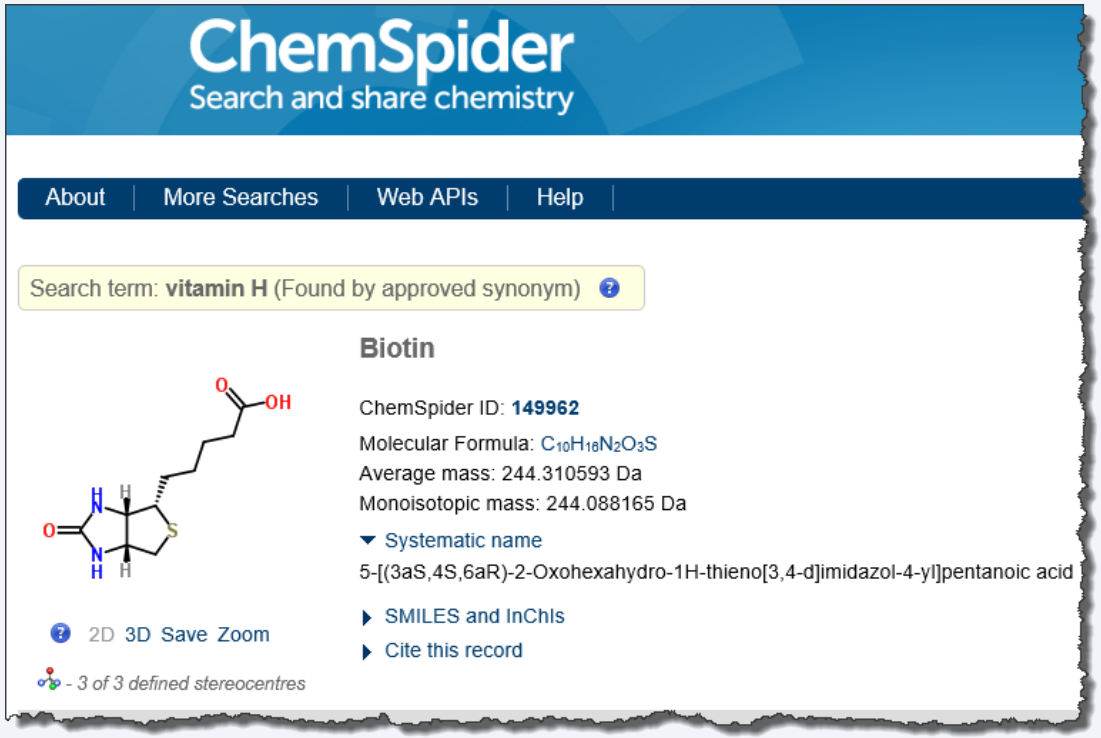

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Computational Chemistry

- Computational chemistry is now widely used to study the fundamental properties of atoms, molecules, and chemical reactions, using quantum mechanics and thermodynamics.
- Computational chemists use mathematical algorithms, statistics, and large databases to integrate chemical theory and modelling with experimental observations.
- Some computational chemists create models and simulations of physical processes, and others use statistics and data analysis techniques to extract useful information from large bodies of data.

Computational Chemistry vs Computer Science

- Computational chemistry is not the same as computer science, although professionals in the two fields commonly collaborate.
- Computer scientists devote their time to developing and validating computer algorithms, software and hardware products, and data visualization capabilities.
- Computational chemists work with laboratory and theoretical scientists to apply these capabilities to modelling and simulation, data analysis, and visualization to support their research efforts.

Tools of a Computational Chemists

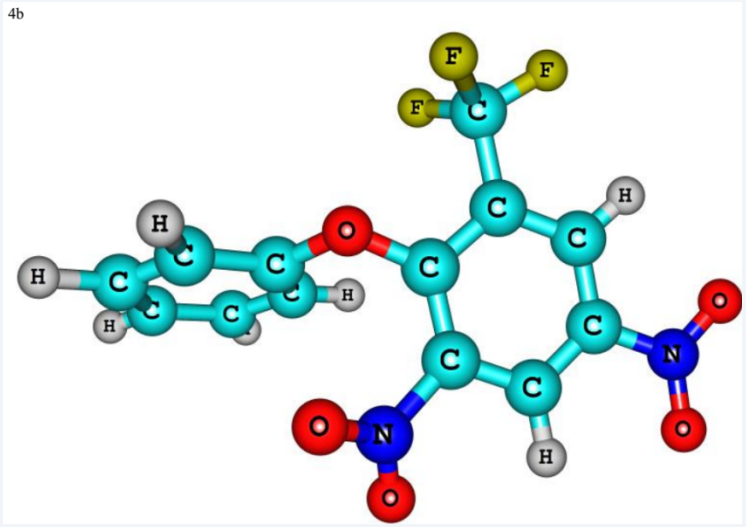
Tools of computational chemists include

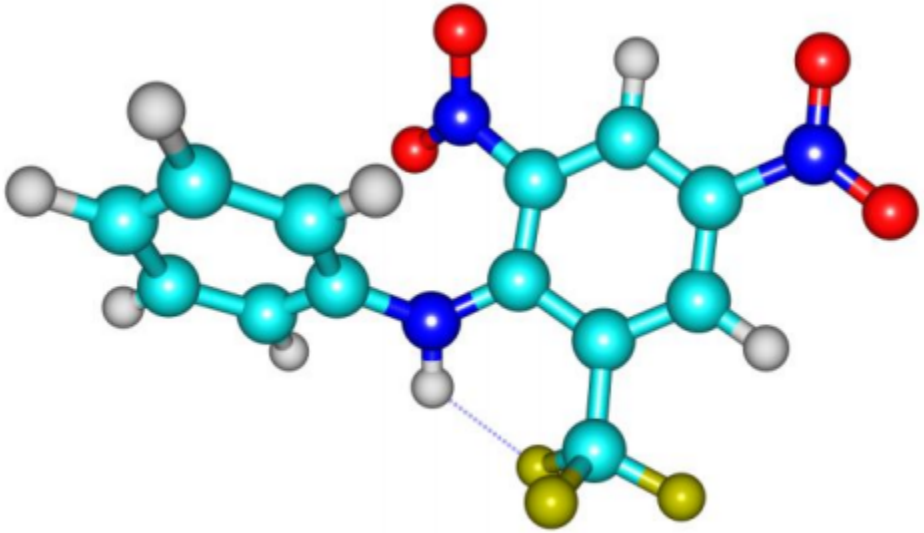
- electronic structure methods,
- molecular dynamics simulations,
- quantitative structure–activity relationships,
- cheminformatics,
- full statistical analysis.

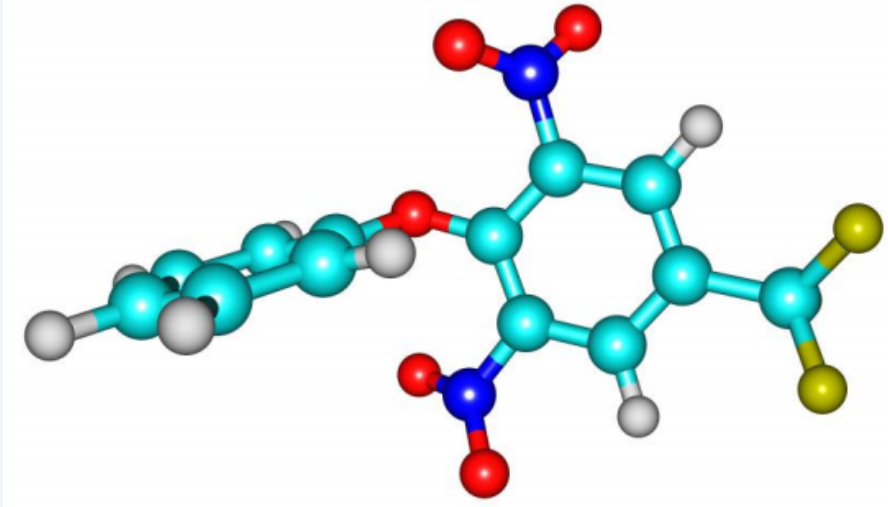
Using computational chemistry software you can in particular perform:

- electronic structure determinations,
- geometry optimizations,
- frequency calculations,
- definition of transition structures and reaction paths,
- protein calculations, i.e. docking,
- electron and charge distributions calculations,
- calculations of potential energy surfaces (PES),
- calculations of rate constants for chemical reactions (kinetics)
- thermodynamic calculations- heat of reactions, energy of activation, etc
- calculation of many other molecular and bulk physical and chemical properties.

Optimized Structures







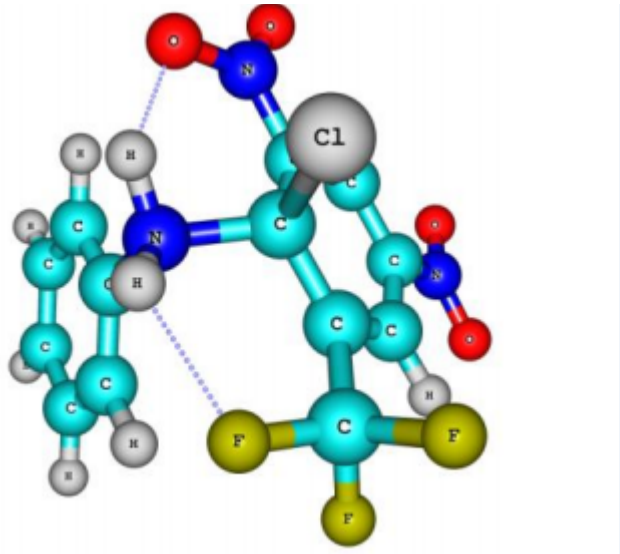


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Table 10. Summary of the energy difference between the 4-substituted and 6-substituted products

	CN	H	CF_3	Ring N
P_{ortho1}	0	0	0	0
P_{ortho2}	4.13	0.48	1.1	9.37
P_{para}	5.33	10.80	0.57	14.14

P_{ortho1} is the product from ortho-substituents with hydrogen bonding between H and NO_2, P_{ortho2} has no hydrogen bonding or with the CF_3 substituents and P_{para} is the product of the 6-substituted reactants. The energy differences were calculated using $P_i - P_{ortho1}$.

Research Article

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Computational studies of the effects of ortho-ring and para-ring activation on the kinetics of S_NAr reactions of 1-chloro-2-nitrobenzene and 1-phenoxy-2-nitrobenzene with aniline

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Computational studies are reported for reactions of 4-substituted-1-chloro-2,6-dinitrobenzenes 1, 6-substituted-1-chloro-2,4-dinitrobenzenes 2 and some of the corresponding 1-phenoxy derivatives 3 and 4 with aniline in the gas phase. The effects of substituent groups in the calculated energy values for reactants 1–4, transition states structures, intermediates and products formed in the reactions between the compounds and anilines have been compared. Calculated bonds length and angles from optimized structures of the reactants were comparable with values reported for some of compounds 1–4 obtained by X-ray crystal structures analysis. Generally, the decomposition of the Meisenheimer intermediate to the products requires more energy compared with the reactants except for when R = H. The order of stabilization of the intermediate was found to reflect the relative order of activation by substituents in the substrates. The 4-substituted-1-chloro-2,6-dinitrobenzenes 1 and the phenoxy derivatives 3 were found to be more stable than their corresponding 6-substituted analogues. This is an indication that the rate of nucleophilic attack at 1-position will increase with increasing ring activation but may be reduced by steric repulsion at the reaction centre that increases in the order Cl < OPh. However, the steric hindrance to the steps involved in nucleophilic substitution by aniline is significantly increased when the substrates contain two ortho-substituents. In most cases, the rate determining step is the decomposition of the σ-adduct intermediate except with 1-chloro-2,6-dinitrobenzenes 1 and 6-substituted-1-chloro-2,4-dinitrobenzenes 2, either because of reduction in ring activation or the presence of bulky ortho-substituents in the chloro compounds 1 and 2. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: nucleophilic aromatic substitution; ortho-ring and para-ring activation; steric and electronic effects; DFT or computational studies

Current Research

- Dinitroanilines and analogues are promising new and inexpensive drug candidates against diseases caused by protozoan parasites.
- Our project is aimed at providing a precise mechanism for the mode of interaction of dinitroaniline-based antiparasitic drug candidates with cellular thiols.
- This interaction is believed to be important to the inhibitory activity of these drugs candidates against protozoa parasites.

Challenges

- Lack of analytical equipment- NMR, Stopped-flow spectrophotometer workstation for fast kinetics.
- Lacked of open access to high performance computing (HPC) resources.
- Acquisition of multi user licensed software for chemical modelling and data analysis.
- Lack of institutional access to electronic data
- Inadequate current literature for teaching and research.
- Poor funding for postgraduate studies.

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