ejpmr, 2017,4(6), 222-225

EUROPEAN JOURNAL OF PHARMACEUTICAL

AND MEDICAL RESEARCH

<u>Review Article</u> ISSN 2394-3211 EJPMR

BEGIN WITH ALPHA EFFECT

*Jimmy Alex

M.pharm, Medicinal Chemistry, JKKM Medical and Research Foundation College, Tamilnadu.

*Corresponding Author: Jimmy Alex

CNCS, PG Dept. of Chemistry, Mekelle University, Ethiopia.

Article Received on 13/04/2017

Article Revised on 04/05/2017

Article Accepted on 25/05/2017

ABSTRACT

The alpha effect refers to the increased nucleophilicity of an atom due to the presence of an adjacent (alpha) atom with lone pair electrons. This first atom does not necessarily exhibit increased basicity compared with a similar atom without an adjacent electron donating atom. The effect is well established with many theories to explain the effect but without a clear winner. The effect was first observed by Jencks and Carriuolo in 1960 in a series of chemical kinetics experiments involving the reaction of the ester p-nitrophenyl acetate with a range of Regular nucleophiles such as the fluoride anion, aniline, pyridine, ethylene diamine and nucleophiles. the phenolate ion were found to have pseudo first order reaction rates corresponding to their basicity as measured by their pK_{a} . Other nucleophiles however reacted much faster than expected based on this criterion alone. These include hydrazine, hydroxylamine, the hypochlorite ion and the hydroperoxide anion. In 1962 Edwards and Pearson (the latter of HSAB theory) introduced the phrase alpha effect for this anomaly. He offered the suggestion that the effect was caused by a transition state (TS) stabilization effect: on entering the TS the free electron pair on the nucleophile moves away from the nucleus causing a partial positive charge which can be stabilized by an adjacent lone pair as for instance happens in any carbocation. Over the years many additional theories have been put forward attempting to explain the effect. A ground state stabilizing effect assumes that the alpha lone-pair and nucleophilic electron pair destabilize each other by electronic repulsion thereby increasing the ground state and making it more reactive. Stabilization of the transition state is possible by assuming some TS free radical character or assuming that the TS has more advanced nucleophile-substrate bond formation. The polarizability of the nucleophile or involvement of intramolecular catalysis also plays a role. One recent in silico contribution did find a correlation between the alpha effect and the so-called deformation energy which is the electronic energy required to bring the two reactants together in the transition state. The alpha effect is also dependent on solvent but not in a predictable way: it can increase or decrease with solvent mix composition or even go through a maximum.

KEYWORDS: Introduction, Reactions of oximes, Intramolecular catalysis, Charge Vs frontier orbital, Transition state hybridisations, Solvent effects, Magnitude of alpha effect.

INTRODUCTION

The alpha effect

- Refers to the increased reactivity of a nucleophile due to the presence of an adjacent (α) atom with a lone pair of electrons.
- Frequently referenced with basicity
- First to attribute enhanced nucleophilicity to the presence of an atom with a lone pair α to the nucleophilic center.
- Relative rates of substitution attributed the abnormal reactivity to increased polarizability of nucleophiles.
- The presence of an α-atom with lone pairs leads to greater nucleophilicity than the basicity would suggest.



The term "the α -effect" was first used by Edwards and Pearson.

Described it as an additional factor influencing nucleophilicity, separate from polarizability. Their hypothesis: Stabilization of the relative electron deficiency in the transition state via π bonding (conceptually similar to carbocation stabilization by a neighboring heteroatom) .Extent of π -donation is greater in nucleophilic addition products than in the conjugate acid, resulting in enhanced stability of the former

Reactions of oximes.

Oxime	$\mathbf{p}K_{\mathbf{a}}$	Rate enhancement ^a
H_2N Me $C=N-OH$	12.9	1.2
Et > C = N-OH	12.60	1.0
Me > C = N-OH	12.42	1.0
$\frac{Ph}{Me} > C = N-OH$	11-48	2.7
Ac $C=N-OH$	9-38	100
Ac C=N-OH	7.38	933

^a Defined as the ratio (bimolecular rate constant for oximate anion/bimolecular rate constant for a phenoxide or alkoxide anion of the same basicity).

Intramolecular catalysis

Some molecules have conformers that minimize $p\pi$ - $p\pi$ overlap



 α -effect attributed to "intramolecular catalysis"

Charge Vs Frontier orbital

Derived perturbation for all interacting orbitals: $\Delta E = -qsqr\Gamma rs + \Sigma m\Sigma nvm - vn + \chi mn$ $2crmcsn\beta rs2\varepsilon mnEm*-En*+crmcsn\beta rs1-\varepsilon mn + \chi mnE$ Am-IPn4

q = charge Γrs = Coulomb term (e2*R*2+ ∂n + ∂m 2) v= orbital occupancy X = constant (2 if both vn and vm = 1, 0 otherwise) $\epsilon mn = 0$ if orbitals are degenerate, 1 otherwise c = orbital coefficients β = resonance integral Eam = Energy lost by removing 1 electron Ipn = Energy gained by adding one electron Em^{*} = Energy of electron in orbital m En^{*} = Energy of electron if it was in orbital n

Transition state hybridization

Some nucleophilic reactions involve a partial electron transfer event. Because of diradical character, α -lone pair stabilizes the transition state



Electronic structure analysis

B

$$N: + S \rightarrow [N \cdot + S \cdot] \rightarrow N - S$$

Alex.

www.ejpmr.com

Hudson proposed that overlap of doubly occupied $p\pi$ orbitals leads to an increase in the HOMO energy .A reaction of such a nucleophile will have decreased $p\pi$ - $p\pi$ interaction in the transition state .The combination of these factors results in the increased reactivity .Some α -nucleophiles might not have the proper orbital symmetry for this interaction.



H00-

- Extent of stabilization will be proportionate to contribution of diradicaloid character:
- Substrates with high electron affinity (lower LUMO) are more likely to undergo an ET event.
- Explains observation of smaller α-effects in Sn2 reactions relative to addition to unsaturated compounds.
- Large β -values associated with ET reactions.
- Dependence of magnitude of α -effect on β agrees with Hudson's work.

Solvent effects

- The magnitude of the α -effect is dependent on β .
- Prior reactions have low selectivity.
- Evident by 20kcal/mol difference in proton affinities.
- It is likely that β approaches 0, so we would expect to observe no α -effect.
- "Determination of β nuc is essential in order to obtain a meaningful conclusion.

2.135

Solvent effect – theoretical study HO – O + Cl = CH3OOH+H OH + Cl = CH3OH+Cl



наан

120 DIHEORAL

8.0

6.0 4.0 2.0

-2.0

'n

60

RHF ENERGY (KCAL/MOL.

The magnitude of alpha effect

- More electronegative α-atoms lead to larger αeffects (FO- vs ClO-)
- Electron withdrawing groups diminish the alpha effect
- Higher electron density at the α-atom and greater positive charge at the electrophile lead to a greater α-effect



CONCLUSION

180 240 ANGLE(DEGREES) 360

сн_ссн

Although the α -effect is heavily modulated by solvent, theoretical and experimental results that the α -effect is an intrinsic property and α -nucleophiles. The physical origin of the α -effect is related to similarities in the electronic structure of the products and the transition state. However, the precise origin of these similarities is still inconclusive.

6.0

Ξ.



REFFERENCES

- 1. www.wikipedia.com
- 2. www.cambridge.in
- 3. William Reusch. "Nucleophilicity & Basicity." *Virtual Textbook of Organic Chemistry* Boundless, 26 May. 2016.
- 4. http://onlinelibrary.wiley.com.