Indian Journal of
Advances in Chemical Science

Article

Structure and Electronic Features of Radicals: Detection and Characterization

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ABSTRACT

Radical reactions occur through the intermediacy of odd electron species and are among the key fundamental classes of organic transformations. Such processes play important roles in mechanistic and synthetic organic chemistry and are essential for many biological and materials applications. In this review, structure and electronic features of radicals of organic molecules have been discussed in details detection and characterization procedure.

Key words: Radical, Intermediate, Molecular orbital, Spectroscopy.

1. INTRODUCTION

In the past two decades, the study of generation of radicals and their chemical as well as biological reactivity has become an area of intense research [1]. Three primary reasons are there behind such interest. The first and foremost is their ability to simultaneously pull off hydrogens from the sugar moiety of opposite strands of a ds-DNA resulting in its cleavage, a process relevant for cancer chemotherapy [1]. In addition, these radicals are useful intermediates for the synthesis of various aromatic compounds including conducting polymers. Their synthesis and methods for their generation under ambient conditions are some other important challenges in this area. In principle, these radicals can be utilized for a variety of purposes. Radicals and radical reactions, in organic chemistry, date back to the early 1800s [1,2] with Kolbe's observation of methyl radicals from the decarboxylation of potassium acetate [3] and the formation of "ethyl" from the reaction of ethyl iodide with zinc first reported by Frankland [4]. Among the most important of these early discoveries is Downes and Blunts' 1879 observation of hydrogen peroxide's decomposition into OH radicals by sunlight [5] and the 1891 discussion of the possible role of radicals in electrolysis by Brown and Walker [6].

Gomberg's 1900 discovery of the highly stable triphenylmethyl radical 1 constituted a major early breakthrough [7,8]. This work and subsequent identification of simple alkyl radicals by Paneth and Hofeditz [9], Paneth and Lautsch [10,11] provided the early foundations of radical chemistry, Scheme 1.

For a more detailed account of the history of radicals in chemistry see "The History of Free Radical Chemistry" [12].

2. STRUCTURE AND ELECTRONIC FEATURES OF RADICALS

Radicals are odd electron species that can be neutral or charged (i.e., radical cations or radical anions). More than one radical center can be present in a molecule (diradicals, triradicals, etc). When the radical site and the ion site are spatially separated on a molecule, such species is referred to as a distonic radical or ion, Figure 1. Extensive research efforts have largely concentrated on mono and diradicals due to their key role in numerous fields including combustion, atmospheric chemistry, interstellar chemistry, polymerization, organic synthesis, and medicinal chemistry. In particular, the explosion of interest in diradicals stemmed from the discovery of natural enediyne antibiotics [13] which are transformed by the Bergman cyclization [14] into reactive diradical species capable of targeting and damaging cancer DNA with astounding efficiency through irreversible H atom abstraction. Latter experimental and theoretical studies [15-18] started to probe distonic ions, sparked by the unusual reactivity of these scarcely studied and exotic species.

In molecular orbital theory, an orbital that holds a single electron is referred to as the singly occupied molecular orbital (SOMO). A common classification separates radicals into two classes: π-radicals occupy predominantly p-orbitals and σ-radicals occupy orbitals with significant contribution of s-character as sp^n-hybrids. The relative amount of p-character generally correlates with the donor ability of radicals. Methyl radical and CH_3CH_2 radical are essentially planar and belong to the π-type, with cyclopropyl and bridgehead radicals being notable exceptions (Figure 2) [19]. Radicals that are substituted with electronegative elements acquire additional s-character, a result of Bent's rule [20-22], for example, trifluoromethyl radical is close to sp^3 hybridization [23]. Vinylic and aromatic radicals are usually σ-radicals [24], although vinyl radicals adopt linear geometry in the presence of acceptor conjugating substituents [25]. Due to their greater partial s-character, σ-radicals tend to be more electrophilic than π-radicals.

The unusual feature of SOMO is its ability to interact in stabilizing manner with both an empty and filled orbital. Interaction of SOMO with the lowest unoccupied molecular orbital (LUMO) of another species is a stabilizing one-electron interaction. Interaction of SOMO with highest occupied molecular orbital (HOMO) of another species is a stabilizing three-electron interaction (Scheme 2). Due to their

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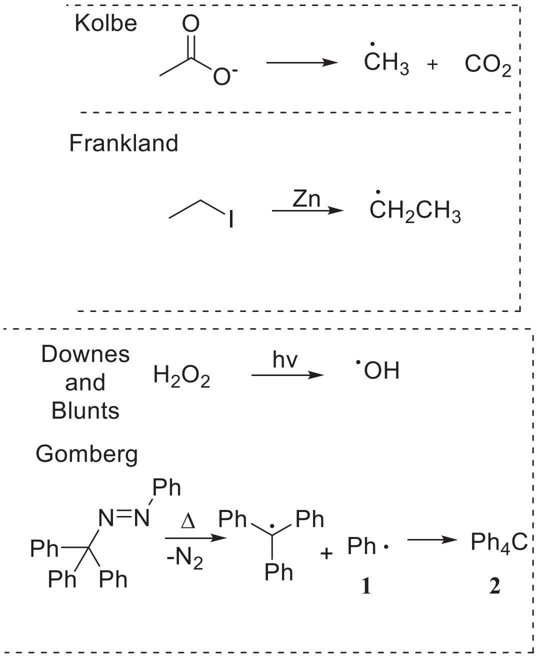
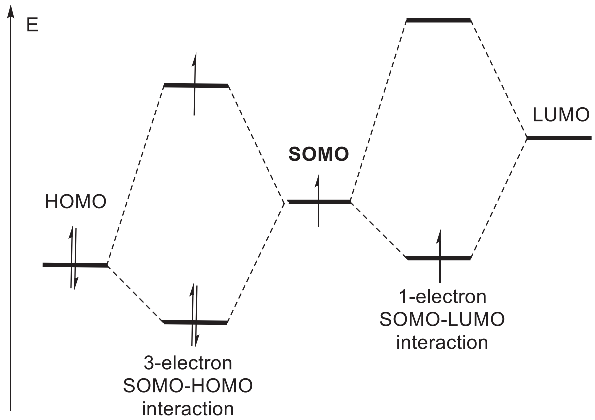
ISSN NO: 2320-0898 (p); 2320-0928 (e)
DOI: 10.22607/IJACS.2023.1103001

Received: 14th April 2023;
Revised: 10th May 2023;
Accepted: 21st June 2023



Scheme 1: History of radical reactions.



Scheme 2: The ambiphilic nature of radical species originates in the net stabilizing SOMO- lowest unoccupied molecular orbital as well as SOMO-highest occupied molecular orbital interactions.

ambiphilic character, the electronic properties and reactivity of radicals are tunable and these species display reactivity towards both electron-rich and electron-poor substrates. As such, polar effects play an important role in the reactivity of radicals, allowing for practical strategies such as Polarity Reversal Catalysis.

Thus, radicals can be stabilized by both electron-withdrawing and electron-donating substituents. The electronic structure of super-stable radicals such as O_2, nitric oxide, and TEMPO reveals the importance of the stabilizing interaction between the SOMO and the adjacent lone pair. Such strong 2-center, 3-electron (2c-3e) interactions correspond to the bond order of ½ between the radical center and the heteroatom and have contributed to interesting transformations [26]. In captodative radicals, the radical center is flanked by substituents of opposite polarity (i.e., a donor and an acceptor). Such radicals [27] enjoy a special stabilization, the extent of which is still under debate [28].

The nature of stabilizing interactions in radical species can extend beyond directly adjacent substituents. In through-bond (TB) interactions, spatially separated orbitals interact through their mutual mixing with the σ orbitals of the intervening framework. Such electronic effects are well-known when both of the non-bonding orbitals are singly occupied, as in 1,4-diradicals. In these systems, TB coupling of radical centers [29] increases the population of the σ^* bridge orbital, ultimately leading to fragmentation into two double bonds. The same effect is responsible for rendering the Bergman cyclization a symmetry-allowed reaction [30] and providing about 3–5 kcal/mol stabilization to p-benzyne [31]. Recently [32], the same TB interaction was shown to stabilize monoradicals. In this case, TB communication between the monoradical and a lone pair three bonds away distinctly stabilizes the radical center, as shown in Figures 3 and 4.

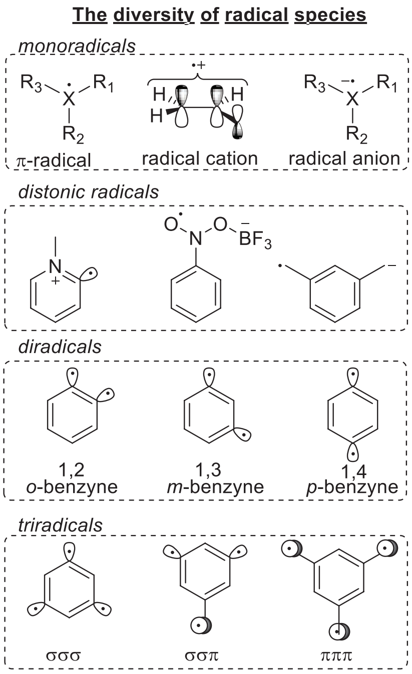


Figure 1: The diversity of radical species.

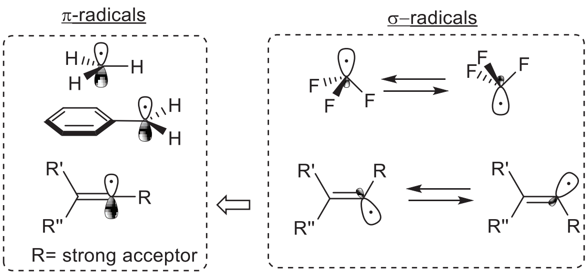
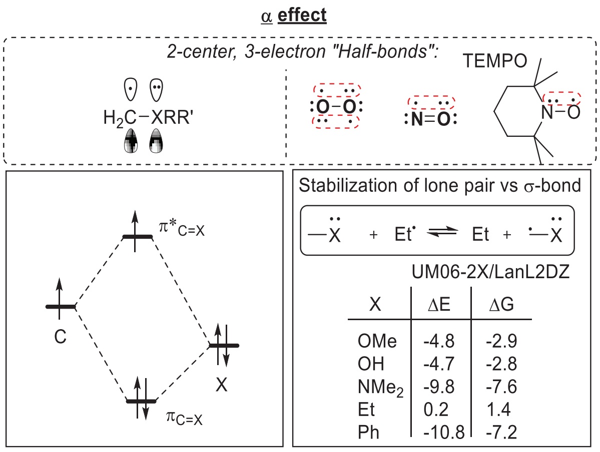


Figure 2: Examples of π and σ-radicals.

3. DETECTION AND CHARACTERIZATION

The detection and characterization of radical species are essential for full understanding their reactivity. Nevertheless, due to their transient nature and corresponding short life-times, characterization of radical species is difficult. First observed in 1994, electron paramagnetic resonance (EPR) spectroscopy has been a primary method for the detection paramagnetic species. If the half-life of the respective radical is too brief for detection, spin traps (commonly nitrone derivatives) are used to trap the radical, converting it into a stabilized, detectible radical adduct. Time-resolved EPR and NMR techniques like chemically induced dynamic electron polarization has allowed real time observation of radicals and radical ions at the nanosecond-to-microsecond time scale, elucidating structural details and insights into reaction kinetics.

Developed by Comisarow and Marshall in 1974 [33], Fourier transform ion cyclotron resonance mass spectrometry has been the standard



X	ΔE	ΔG
OMe	-4.8	-2.9
OH	-4.7	-2.8
NMe$_2$	-9.8	-7.6
Et	0.2	1.4
Ph	-10.8	-7.2

Figure 3: The α-effect: 2-center, 3-electron interactions are stabilizing "half-bonds" present in many important molecules, calculated at UM06-2X/LanL2DZ level of theory.

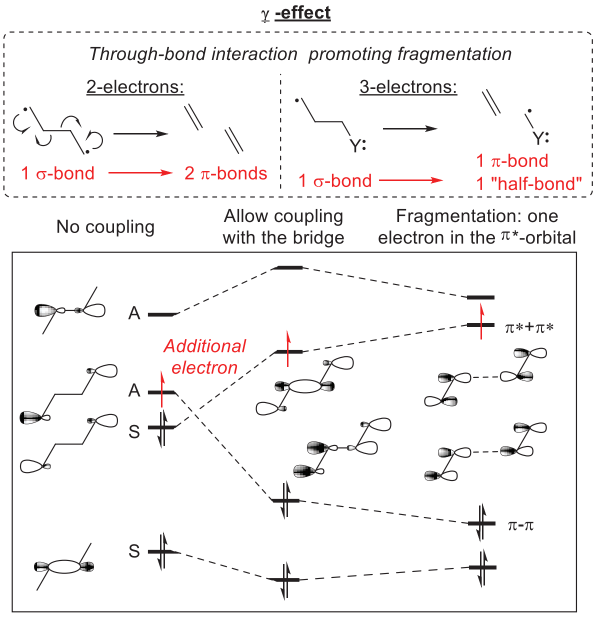


Figure 4: The γ-effect: TB electronic coupling between non-bonding orbitals in 1,4-diradicals promotes fragmentation. Fragmentation of γ-heteroatom substituted monoradicals is less favorable.

technique for the study of gas-phase ion-molecule reactions, enabling the isolation of radical ions and distonic ions and, in turn, kinetic studies.

Low temperature matrix isolation has enabled direct IR spectroscopic detection of very reactive intermediates, such as *o*-benzyne, since the 1970s. In inert media (Ar, Ne) at cryogenic temperatures (below 30 K), radicals are immobilized and kinetically stabilized. Such methods continue to grow in sophistication; for example, the development of high-resolution rovibrational spectroscopy matrix isolation techniques where reactive radicals frozen in helium droplets has allowed the isolation and characterization of many radical species [34,35] and, in some cases, investigation of bimolecular reactions of the isolated species with small molecules.

4. CONCLUSION

Thus, in the nut cell, we can conclude that radical reactions occur through the intermediacy of odd electron species and are among the key fundamental classes of organic transformations. Such processes play important roles in mechanistic and synthetic organic chemistry and are essential for many biological and materials applications. Radical reactions can often be carried out in the presence of sensitive functionalities, under mild conditions, and with significant regio- and stereo control. Hence, the better we understand its structure and property, they can be utilized more to serve mankind.

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