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Stability, reactivity and dynamic study of switchable intermolecular hydrogen bonding in dinitrobenzene isomers: A theoretical – Experimental approach

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ABSTRACT

Among several non-covalent weak interaction(s), hydrogen bonding is predominantly considered as a key factor in some biological events i.e. information transfer at intra cellular and/or intra/inter organelle level. Dinitroaromatics contain $-NO_2$ group(s) which strongly facilities electron and/or proton transfer, could be envisaged to be used as an active group in a drug molecule. We have decided to investigate dinitroaromatics as model substances for the following reasons (a) low reduction potential, (b) multi-electron accepting ability of NO_2 groups, (c) formation of stable anion radicals and dianions. Linear scan and cyclic voltammetry were used for study. It was found that DNBs in the presence of HB-agents exhibit switchable H-bonding *via* electro-reduction steps and formation of $DNB^{-\cdot/2-}\cdots(HB)_{n\ or\ m}$. HB strength significantly perturbs chemical equilibrium and/or kinetic process, hence, an array of strong, intermediate and weak type interactions was considered for investigation. Experimental values of stability constant, K_{eq}, rate constant of formation of H-bond, *k*, and number of bonds formed were evaluated for corresponding process(es) (i) $DNB^{-\cdot} + n[HB] \rightleftarrows DNB^{-\cdot}(HB)_n$ and (ii) $DNB^{2-} + (m-n)[HB] \rightleftarrows DNB^{2-}(HB)_{m-n}$. Values of K_{eq} for processes (i) and (ii) were found to be within the range of 1.9 –9.0 M^{-n} and 7.0–9.4 $\times 10^4$ M^{-m}, whereas, *k* values were moderate to high as 0.23–26.1 $M^{-n}.s^{-1}$ and 3.3 –6.5 $\times 10^6$ $M^{-m}.s^{-1}$, respectively. A more plausible assumption is the existence of 1:1 or 1:2 associates between $(X)DNB^{2-}$ (where, X = 1,2-,1,3-,1,4-) and HB-agents. Quantum chemical calculations were carried out for $(X)DNB^{-\cdot/2-}\cdots(HB)_{n\ or\ m}$, *vis-a-vis* geometry optimization leading to better understanding of structural array in three dimensional space.

1. Introduction

Intra- and inter-molecular hydrogen bonding considered to be a non-covalent, weak interaction, have been a subject of interest for many decades [1–5]. Non-covalent weak interaction(s) are considered as an important phenomenon for host molecule energetic and structural properties in complex chemical/biochemical systems, such as protein folding, (un)zipping of DNA, crystal packing in organic solids, etc. Weak interactions in drug can increase binding affinity and specificity of a drug molecule. This may presumably be a fundamental key to unlock the possibility of rational drugs design [6,7]. Hydrogen bonding (H-bonding), π-π stacking, O-H/π, interactions, etc., can stabilize the association e.g., the drug acceptance (for symptoms of Alzheimer's disease) with particular enzyme receptor. H-bonding is most likely an obligatory prerequisite for several drugs–receptor interaction(s). Therefore, there is an ever increasing interest in exploring the existence, studying the nature, and computing the strength of H-bonds [8–11].

H-bonding process may very well depend upon (i) the nature and structure of H-bond acceptor (dinitrobenzene anion radical/dianion), (ii) H-bond donor i.e. protic agents, and (iii) media. Additionally, the stability, reactivity and structure of complex $((X)DNB^{y-}\cdots(HB)_{n\ or\ m}$; where y- = 1- or 2-, *n* or *m* means H-bonding number) certainly need to be investigated. In this connection a series of reactions, from protonation to H-bonding is to be studied experimentally. At present, there are number of techniques such as: electrochemical, spectro-electrochemical, spectrophotometric,

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vacuum techniques, shock tube method, flow cell etc., available which can be used to generate free radicals, and radical ions to study their reactions. Among electrochemical, *in situ* linear scan voltammetry (LSV) and cyclic voltammetry (CV) are considered to be the most preferred techniques to study H-bonding process [12,13]. These are simple and elegant techniques providing the information on the dynamics of such electrochemical reactions as switchable H-bond formation.

In present study, the H-bonding equilibrium process was followed through determination of H-bonding equilibrium constant (K), the rate constant of H-bonding process (k) and number of H-bonds formed per molecule (*n*, *m*). Thus, the exploration of kinetics and dynamics of a switchable H-bonding process, otherwise important and challenging task, is the focus of this work. To understand the kinetics as well as dynamics of switchable intermolecular H-bonding, a comprehensive study on a particular system must be carried out to evaluate all these parameters. Surprisingly, this area has remained totally untouched so far.

Nitroaromatics encompass a large class of organic redox active substances and they are usually found in particulate emission from many combustion sources, most notably in diesel exhausts. Despite the concern about their harmful effects, they also offer potential use in medicine and cancer therapy [14]. Dinitroaromatics having two electrons accepting sites seems to be even better therapeutic candidates. However, and surprisingly, drugs containing nitro based active unit(s) are rarely found in the market [15]. Nitroaromatics, most particularly dinitroaromatics, having lower redox potentials, and thus easily forming anion radicals and/or dianions can perhaps offer an interesting possible addition to medical therapy.

In optimizing a drug-receptor interaction few questions arise which are; (a) instead of using "hard drugs" why not to use "soft drugs" with little side effects; (b) does the nature of (covalent/non-covalent or weak) bonding affects the drug–receptor interaction; (c) how many interaction(s) taking place i.e. how many H-bond(s) are formed per molecule; (d) what sort of mechanism is followed by the active participant i.e. nitro-group(s) - to form H-bond(s), and (e) how are such interactions affected by substituent(s) and their position(s)?

Nitro-/dinitroaromatics present well-studied example of organic redox couple and act as an electron shuttle between two reduced states [16–20]. Their reduced species exhibit pronounced H-bonding as well as protonation with various protonating agents such as water, alcohols, urea, aniline, etc. Stability and kinetics of H-bonding process, though important, has, so far, attracted just marginal attention of researchers. It should be noted that a dinitrobenzene (DNB) molecule has four electron attracting centers (four "O" atoms), thus exploration of the geometry of H-bonded complex becomes an interesting aspect for study.

Irrespective of neutral H-bonding, electrochemistry reveals the formation of charge induced H-bonding. This phenomenon was observed in the case of interaction of reduced substrate with −OH and −NH based hydrogen bonding (HB) agents representing classical type O-H···O/N interaction(s) [21]. In this context some studies on quinones and nitro-/dinitroaromatics [22,23] have been done in recent years. Anion radical and dianion, in general, can form inter as well as intra molecular H-bonding [12,13,24–27]. Changes in physico-chemical properties of anion radical and dianion of dinitroaromatics could be reversibly achieved by incorporating non-covalent interaction, e.g., H-bonding. This reversible shuttling due to H-bonding induces a protic molecule to interact with a dinitroaromatic substrate to form a reduced molecular assembly. The above proposed strategy is worthy of investigation in rational drug design.

This study is particularly concerned with H-bonding phenomenon which has been implicated in biological function of (1,2-, 1,3-, 1,4-)DNB system and on which, surprisingly, little systematic work has been done so far [13,22]. Bu et al. [13] investigated H-bonding equilibrium process in anion radicals of DNB with aryl urea. However, no information, on kinetics, dynamics, the number of H-bond(s) formation, and the three dimensional space structure of H-bond(s) formation has so far been reported, even though the significance of this information is apparent. In this context systematic but only limited work on anion radical of 1,3-DNB has been reported earlier by Mohammad et al. [22].

Regarding the stability, reactivity and dynamics of H-bonding process in (X)DNB^{y-} (where X means 1,2-, 1,3-, 1,4-DNB and y-means 1- or, 2-), some physical parameters, such as, H-bonding equilibrium constant, kinetics factors and their structural constraints are important. This information helps in understanding the existence and nature of non-covalent process, under both protic- and aprotic-, hydrophobic (e.g. enzymatic-pockets) environment in (bio)chemical reactions and drug-receptor interaction(s). Moreover, this investigation is combined with an appropriate quantum chemical analyses to describe inter- and intra-molecular forces relevant to this subject matter. Therefore, theoretical computational study is envisaged to explore (X)DNB^{y-}···HB interactions.

LSV and CV together with digital simulation are most suitable techniques for generating and monitoring radical intermediates and their reactions. These techniques have been previously employed in order to study equilibrium process [12,22,23]. At the same time, classical theory proposed by Nicholson and Shain [28], which deals with chemically coupled electrochemical processes for stationary electrode voltammetry (e.g. LSV and CV) have been further explored by Gupta Linschitz [12] and Mohammad et al. [22,23]. Moreover, through this technique one can obtain the number of H-bonds formed. Hence, this technique LSV or CV in conjunction with simulation of voltammograms has been employed here to evaluate the various parameters and follow the dynamics of H-bonding.

2. Experimental

2.1. Instrumentation

All electrochemical measurements were done on CHI-600 series Electrochemical Analyzer along with CHI-600C software [29]. Three electrode assembly from BAS*i* (West Lafayette, IN, USA) [30] was used for LSV and CV. Glassy carbon electrode (GCE) with an area of 0.0706 cm^2 was used as working electrode. Polishing with alumina or fine diamond polisher was used to clean GCE surface. Silver-silver ion (Ag/Ag^+) electrode was used as reference electrode, $AgNO_3$ (5 mM solution with 0.1 M tetra-n-butyl ammonium perchlorate) in acetonitrile was freshly prepared for each experiment. A platinum coil 23 cm in length with 0.5 mm diameter was used as a counter electrode.

A double walled electrochemical cell MR-1212 supplied by BAS*i* was used. The cell cover contained five holes, three for electrodes, remaining two for argon gas bubbling inlet and outlet. Constant temperature throughout the experiment was maintained by connecting electrochemical cell to a circulating thermostat bath supplied by Daihan Lab Tech Co., Ltd.

2.2. Material

All chemicals were HPLC/analytical-grade purified as practiced: Acetonitrile (CH_3CN) from Fisher Scientific Co. was used as solvents after drying over 3 Å molecular sieves to remove traces of remaining water and further passing through alumina column. Methanol (MeOH), ethanol (EtOH), 2-propanol (2-PrOH), ethylene glycol (EtGy) > 99.99% pure were purchased from Fischer Scientific