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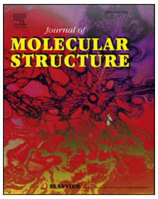

On the [2+2] cycloaddition reaction of configurationally locked polyenes – An experimental and theoretical study

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ABSTRACT

This paper provides experimental and theoretical study of reaction of [2 + 2] cycloaddition of substituted α–unsaturated isophorone dyes, involving high resolution electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) tandem mass spectrometric (MS/MS) analysis in solution and in gas–phase (GP) of substituted 3-[2-(X-substituted-phenyl)-vinyl]-5,5-dimethyl-cyclohex-2-enone and configurationally locked polyenes (CLP). The *ab initio* and density functional theoretical (DFT) examining provides information about molecular geometry, thermodynamics, kinetics and ionization potentials of sixty six isomers of dimeric dyes, including corresponding *cis*-anti-*cis* and *cis*-syn-*cis* head-to-tail and head-to-head forms. The comparative collision induced dissociation (CID) or collision activated MS and theoretical analyses carried out bring light *into* the mechanisms of competitive dimerization within the frame of 3-[2-(X-substituted-phenyl)-vinyl]-5,5-dimethyl-cyclohex-2-enone; molecular and environmental factors governing regioselectivity of reaction. The analyses involve both qualitative and quantitative kinetics and thermodynamics of experimental MS data along with corresponding theoretical examining of CLP dimers. As far as 3-[2-(X-substituted-phenyl)-vinyl]-5,5-dimethyl-cyclohex-2-enone and CLP dyes have already found an industrial scale application as non-linear optical materials (NLO) for THz wave generation and detection as well as pharmaceutics for treatment of and preventing of neurodegenerative diseases, this study has a strong transdisciplinary impact to many research fields as well as to still not well understood, but crucial to fields of organic synthesis and catalysis, molecular level fundamentals of chemical reactivity in gas– and condense phases. Following the latter lines of contributions of the work, we might hopefully expect that the prospective highlighted in this study should inspired further research effort devoted to correlative quantitative thermodynamic and kinetic CID mass spectrometric and quantum chemical analyses, which allow to improve the reaction effectiveness depending on the complexity of the wanted CLP scaffolds.

1. Introduction

Isophorone (3,5,5-trimethyl-2-cyclohexen-l-one, Scheme S1) serves as a particularly important chemical intermediate to the synthesis of various multifunctional materials, largest part of which have found industrial scale application to many branches [1–3]. The review of the relevant literature in the field shows the following implementations. Isophorone derivatives such as, for example, 2-{3-[(*E*)-2-(dibutylamino)-1-ethenyl]-5,5-dimethyl-2-cyclohexenylidene}malononitrile ones have been utilized as highly efficient polymeric photorefractive composites [1(a)]; isophorone diisocyante is used to preparing of modified cellulose nanocrystals, involved into industrial manufacturing of paper, ropes, textiles, and fibres [1b]; polyarylates applied as membranes for gas–separations [1c]; selenophenes obtained *via* five-member ring heteroaromatic formation at C4–C5 positions in the isophorone scaffold [1d]; or isophorone based fluorescent dyes of CLP type as colorimetric and radiometric palladium censoring systems [1e], respectively. The latter derivatives have attracted much attention as potential NLO materials for photonic devices, THz wave generation and detection materials; optical parametric oscillation and frequency conversion [1f,g,i]. At an industrial scale of application the crystal of crystal 2-(3-(4-hydroxystyryl)-5,5-dimethylcyclohex-2-enylidene)-malononitrile has already found

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place as THz–generating NLO device [1h]. CLPs have also found application to the pharmaceutical industry as corresponding biologically active pyrazole containing derivatives, obtained *via* Swern oxidation [2a]. Potential application of functionalized 3-[2-(X-substituted-phenyl)-vinyl]-5,5-dimethyl-cyclohex-2-enones as anti–oxidants and anti-ischemic agents has been reported, too [2b]. Their clinical application for treatment of and preventing of neurodegenerative diseases has been highlighted in Refs. [2c,d]. To the field of biology, those substances have found place as solid–state fluorescent dyes showing efficient red–emission, thus making them suitable imaging materials [3a,b] as well.

Much of the literature on synthetic organic chemistry highlights the importance of isophorone as an intermediate. And this is associated not only with the facts that it is a cheap and commercially available reagent. In addition, isophorone exhibits great chemical reactivity tolerating a large number of substitution reactions [4]. For example, it forms isoxylitones *via* aldol condensation with acetone yielding to new derivatives at C^9– and O^{10}–positions [4a]; 3,4-dihydro-2H-naphthalen-1-one molecular scaffold *via* interaction with mesityl oxide; substituted phenols; acidic catalysed photochemical de-conjugation reaction yielding to cyclic products to C^4–C^5 centres [4b]; C^5–C bond formation via Suzuki-Miyaura coupling reaction [4c]. Isophorone participates in the reaction of Claisen–Schmidt condensation yielding to C^2–substituted derivatives, interacting with aromatic aldehydes [5]. It readily participates in photo-induced [2 + 2] cycloaddition reaction yielding to dimers (Scheme S1) [6]. Due to the general importance of reactions of α–unsaturated enones to many biological phenomena, in general, the dimerization reactions of isophorines, in particular, focusing the attention on the regiselectivity of the reaction, have been objects of broad analysis both in homogeneous solution; in micellar solutions as crude biomimetic models [6a,h]; in porous crystalline host [6c,d]; in supercritical medium [6e], respectively. Isophorone molecular scaffold is involved in many naturally occurring products such as for example the plant hormone abscisic acid [6g]. In spite of the large scale of applicability of isophorone derivatives to numerous branches of the industry; it importance to the organic synthesis and enormous research efforts in the field of organic synthesis associated with photodimerization of isophorone, actually, for over three decades, there have been only few experimental studies dealing with the [2 + 2] cycloaddition reaction producing dimers, however, many fundamental questions about the mechanisms of this process remains poorly understood. Not enough has been done to understand the correlation between the electronic structure and the chemical reactivity of the isophorone depending on environmental factors like pH, UV–irradiation, T, P, ionic strength and more. One of the basic reason of this rather lack of knowledge about the chemical reactivity of isophorone is associated with the fact that the research efforts have been concentrated on the improvement of regioselectivity of reaction of dimeric products, because of the goal of the studies is an applied oriented synthesis, furthermore, at an industrial scale of application [1–3]. This point has been made to emphasize that there is a significant empirical knowledge about the large scale of different chemical products of isophorone. However, this empirical support urgently calls for a comprehensive complementary theoretical and experimental treatment of the chemical reactivity of isophorone, in order, to understand the molecular level mechanistic aspects of the reactions. It should be stressed that most of our effort focusing on new CLPs has also been connected with only applied oriented aspects, thus reporting a new type chemically substituted derivatives as potential THz generating NLO materials and their theoretical prediction of linear and non – linear optical properties [1g]. However, the problematic associated with the molecular level mechanism of the chemical reactions is of fundamental importance to the optimization of the chemical reactions. Because of it provides a correlation between the molecular and electronic structures as well as chemical reactivity. In this context, the article [1g] is based mainly on those CLPs derivatives, which have been isolated at good–to–excellent yields thus aiming their further crystallization and structural elucidation. Considering the data in Ref. [1g] dealing with the applied aspects of the new functionalized CLPs, there has been excluded results about observable large number of competitive reactions, of significant importance to the chemical synthesis of CLPs. This is a common trend of studies of CLPs, which have increased considerably, but despite the fact that they become even more numerous, they have kept the applied–oriented impact [1]. Nevertheless, it should be pointed out, that in describing mechanistic aspects of chemical reactions of CLPs the complexity of the molecular scaffolds require implementation of a complex theoretical and experimental strategy for treatment of the electronic structure and chemical reactivity. We now examining this problematic, reporting new mass spectrometric and theoretical quantum chemical data about the dimerization reactions of functionalized isophorone based dyes (Scheme S1), which first in the literature bring light on the molecular engineering of the formation of dimers and the factors governing the regioselectivity of this process. We have provided a comprehensive analysis of the molecular and environmental factors determining the thermodynamic stability of those dyes, thus allowing further optimization of the synthetic schemes for obtaining of multifunctional derivatives based on isophorone, gaining maximum efficiency, good–to–excellent yields, high stereo-selectivity and mild experimental conditions. Our response to the lack of comprehensive understanding about the molecular level mechanistic aspects of the chemical reactivity of isophorone and its derivatives consists on: *(i)* Study of the energetic of statistically represented number of possible interaction modes causing for formation of dimeric dyes, in addition, taking into consideration the *cis*-anti-*cis* head-to-tail, *cis-syn-cis* head-to-tail, cis-syn-cis head-to-head and cis-anti-cis head-to-head isomers; *(ii)* Examining of the environmental and molecular effects on the reaction kinetic and thermodynamics both experimentally – by the CID mass spectrometry – and theoretically. There are taken into consideration the effect of the temperature, type of the solvent and the salt effect (ionic strength effect with a range 0.01–0.1 mol dm^{-3}); *(iii)* Theoretical analysis of the chemical reactivity of the dyes, including reactions in gas–phase. The nature of the C–C bond in cases of hyper-conjugated compounds is examined as well. At this level of investigation we explicitly focus the study on the unique nature of the chemical bonds of the latter aromatics and their reactivity, because of there is found different behaviour of the hyper-conjugated organics in the gas– and condense phase. In view of the increasing more recent application and great significance of CLPs to many branches of the industry [1–3], our observations about the correlation electronic structure – chemical reactivity of highly functionalized dyes treated in this paper have great both fundamental and applied impacts to the fields of organic synthesis and catalysis; materials research of NLO phores; linear optical fluorescence imaging reagents for diagnostics; and materials for medicinal purposes, including pharmaceutics.

2. Experimental

2.1. Materials and synthesis

Isophorone was purchased from Sigma–Aldrich (Germany). The 4-morpholin-4-yl-benzaldehyde, 4-dimethylamino-benzaldehyde and 4-pyrrolidin-1-yl-benzaldehyde were also Sigma–Aldrich