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On the mechanism of the photocyclization of azadienes

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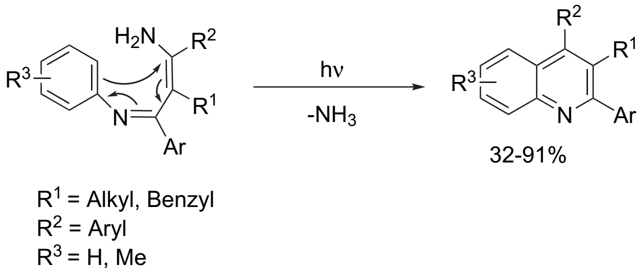
ABSTRACT

The photocyclization of azadienes to yield quinolines has been studied by means of CASPT2//CASSCF calculations. In order to study this extensive family of compounds, a minimal model system keeping the fundamental key features of this kind of compounds have been analyzed with the aim of explaining the general behavior of azadienes found experimentally. We show that, although several conformers of the reacting molecule are populated on the ground-state at room temperature, there is only one capable of successfully yield the products. It is shown that photocyclization takes place with fast relaxation in both S_2 and S_1 excited states, in agreement with the experimental lack of fluorescence. This fact, together with the presence of reaction paths that allow effective recovery of the starting molecule, explains not only the experimental photocyclization of azadienes under UV radiation, but also accounts for the low efficiency of the process. The mechanistic information obtained allows to provide an explanation of the found reaction outcome and to suggest some modifications to improve the synthetic utility of these reactions.

1. Introduction

The quinoline ring system has received considerable attention, as many natural products with interesting properties include this substructure, specially alkaloids.[1] Based on these compounds, many synthetic products also contain the quinoline moiety, such as chloroquinone, an antimalarial compound, quinolone, with high antibacterial activity and acridine derivatives used as antipsychotics.[2] Thus, a number of methods have been developed to synthesize these structures.[3–6]

We have previously reported[7–12] the photochemical synthesis of different quinoline derivatives under mild reaction conditions with good chemical yields, including haloquinolines, benzoquinolines and pyridine derivatives (Scheme 1). This methodology allowed us to synthesize with ease a wide range of compounds in good yields. However, the applications of this approach to these families of compounds have a serious drawback: the low efficiency of the process. In general, although the final compounds were obtained in good yields, the irradiation times were usually too long for the concentration and absorption of the reacting species. Thus, competitive processes occurred as starting material decomposition and/or polymerization were found in most cases. In order to turn this synthetic method into a more convenient entry route to a whole set of compounds, the generality and ease of this reaction should be maintained while the efficiency should be increased to minimize the effect of side reactions.



Scheme 1. Photochemical synthesis of quinoline derivatives.

A detailed understanding of the processes taking place after light absorption is necessary to control the reaction course before any practical modification could be envisaged. Thus, here we present a complete computational study of the reaction together with some complementary experimental data.

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2. Computational methods

The MP2//HF methodology was employed to analyze the ground-state conformers of model A (see Fig. 1), determining minimum energy structures at the Hartree–Fock level, followed by single point-energy correction applying second-order Møller–Plesset perturbation theory. After optimizing model B and C at the MP2 level, we have employed 3-states averaged for S_2 and 2-states averaged for S_1 SA-CASPT2//CASSCF (State-Averaged Complete Active Space Self Consistent Field with Perturbation Theory to Second Order) methodology for the determination of the reaction paths.[13] The selected active space is formed by 12-electrons-in-11-orbitals for model B (see Fig. 1), and by 8-electrons-in-7-orbitals for model C, i.e., all π-type electrons plus the lone pair of the nitrogen in the ring (N_3), and the corresponding π-type orbitals and 1n orbital, with a 6-31G(d) basis set. The second nitrogen is not included in the active space, since it does not contribute significantly (the orbital occupation number is close to 2.0 when including it in the active space) to the proper description of the studied electronic states. All the optimizations have been performed by using analytical CASSCF energy gradients, while single point CASPT2 calculations (with CASSCF weight reference around 0.7) have been employed for key structures, in order to account for the dynamic correlation. Analytical CASSCF hessians have been also computed when frequency calculations were needed. In order to compute reaction paths, Intrinsic Reaction Coordinates (IRC) have been determined.

The topology of the conical intersections (CIs) was determined by performing a scan around the CI for the corresponding electronic states. Concretely, a loop of radius equal to 0.05 Å, formed by 20 equally spaced structures, has been determined for each CI described in the text. These structures were generated as a linear combination of the computed Gradient Difference (GD) and Derivative Coupling (DC) vectors, which define the 2-dimensional subspace where the energy degeneracy is broken.[14]

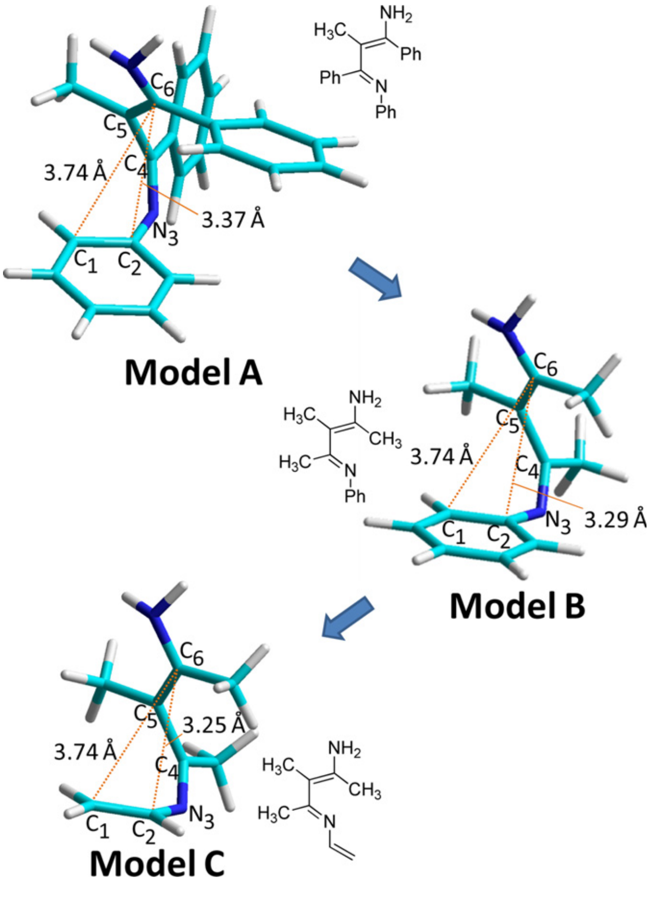

Fig. 1. Selected conformation of the molecular system (model A) by MP2//HF conformational study; MP2 optimized model resulting from substitution of phenyl by methyl groups (model B); MP2 optimized model system (model C) employed in the study of the photoreactivity, formed by replacing the imino-phenyl by an imino-vinyl group, keeping restrained the C_1–C_6 distance (3.74 Å) between the centers giving the formation of the σ-bond during the photocyclization.

In order to study the relaxation processes from a given CI, two methods have been employed. The first, applied to all CIs, consists in the computation of a set of Minimum Energy Paths (MEPs) starting from each of the 20 structures of the loop around the CI, as described above. The second method, employed in some cases, consists in the calculation of Initial Relaxation Directions (IRDs),[15] which is based on a full optimization of the molecular structure subject to a fix distance to the tip of the CI. This method permits the estimation of proximity of a given valley on the potential energy surface to the CI, finally leading to some photoproduct. This proximity (distance to the CI) can be taken as a measure of the feasibility of each path.

3. Experimental

Luminiscence spectra were recorded at room temperature with a Jobin Yvon Horiba Fluorolog 3-22 Tau-3 spectrofluorimeter. Data was analyzed with the Origin 6.1 program. Fluorescence lifetime recording was performed with a 280 nm Horiba Jobin Yvon-IBH NanoLED excitation Source with a nanoLED controller module HJY-IBH FluoroHub-B. The fluorescence quantum yield was measured with a Jobin Yvon Horiba Fluorolog 3-22 Tau-3 spectrofluorimeter equipped with an F-3018 integrating sphere accessory (Horiba Jobin Yvon-IBH). The reaction quantum yield was measured irradiating at 334 nm with an Oriel Cornestone 130 1/8 m monochromator and a 500 W Hg arc lamp placed in a proper lamp housing, being the samples placed in quartz cuvettes (1.0 cm path length). UV–vis spectra were recorded by a Hewlett–Packard HP 8451A Diode Array UV–vis spectrophotometer. Quartz cuvettes (1.0 cm path length) were used for the measurements. Gas chromatography/mass spectrometry (GC/MS) measurements were performed with a Hewlett–Packard HP G1800B GCD System.

4. Results and discussion

4.1. The model system

As shown in Scheme 1, photocyclization of azadienes to yield quinolines bears the presence of different alkyl, aryl, and heteroaryl substituents on the structure. Although this affords great synthetic versatility, theoretical calculations of molecules with such substituents would cause an unnecessary computational cost, as it has been experimentally shown that most substituents can be simple H or methyl groups. As a first simplification we explored the 3-methyl-2,4-diphenyl-4-amino-phenylimine (Fig. 1, model A) bearing two phenyl groups in positions 2 and 4. A conformational study was performed by using MP2//HF methodology. The selected structure was the lowest in energy among the ones showing correct orientation of the carbon atoms involved in the photocyclization, i.e., the formation of the C_1–C_6 σ-bond (C_1–C_6 distance=3.74 Å). This corresponds to a geometry 1.77 kcal mol^{-1} higher in energy than the global minimum, which can be populated through a transition state (TS_1 in Scheme 2) lying 6.8 kcal mol^{-1} above the global minimum, where the C_1–C_6 distance enlarges to 5.18 Å (see Supplementary data for details). This is in agreement with available experimental data reporting low efficiency for the photocyclization process,[7–12] since the most stable structure does not favor the process, but a suitable geometry (Fig. 1, model A) can be easily reached at room temperature.