Transannular Interactions in N-Aryl-5-azocanones, A Semiempirical Quantum Mechanics and UV Spectroscopy Studies ☆

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ABSTRACT: *The ability of the present semiempirical quantum mechanics methods are surveyed for reproducing the transannular interaction in the bifunctional N-phenyl-5-azocanones. The AM1 method is the best with the order of reliability being AM1, PM3, MNDO and MINDO/3. AM1 calculations were then carried out for quantification of transannular interaction. The $n_{(O)}$ ionization potential has been used for this purpose. A linear correlation is found between the $n_{(O)}$ ionization potential and the Hammett substituent constant (σ). The UV spectroscopy was used to study the transannular bond formation in N-aryl-5-azocanone derivatives.*

KEY WORDS: *Transannular interaction, Semiempirical quantum mechanics, Eight-membered rings, Tautomerization, Azocanone*

INTRODUCTION

The medium-sized ring molecules (8-11 membered rings)adopt conformations in which certain ring atoms may be close to each other. If two functional groups of the donating and accepting nature are introduced at suitable positions, transannular interaction and reaction of functional groups may happen[1]. Transannular interactions have been discovered in alkaloids and investigated by chemical, spectroscopic(IR, UV, ORD) and other physical methods in the 1950's [2]. Studies of the properties of these functional groups and their mutual interactions have been the subject of extensive research works[3].

Transannular electronic interactions are mainly studied by photoelectron spectroscopy (PES) and MNDO calculations [4,5]. Also the IR and ^{13}C-NMR spectroscopic methods [6] have been used for investigating the transannular nitrogen-carbonyl interaction in medium ring compounds. In substances having the nitrogen as a donor and carbonyl group as an acceptor, MNDO calculations

☆ *Dedicated to Professor Mahdi Golabi on the occasion of his 67th birthday.*

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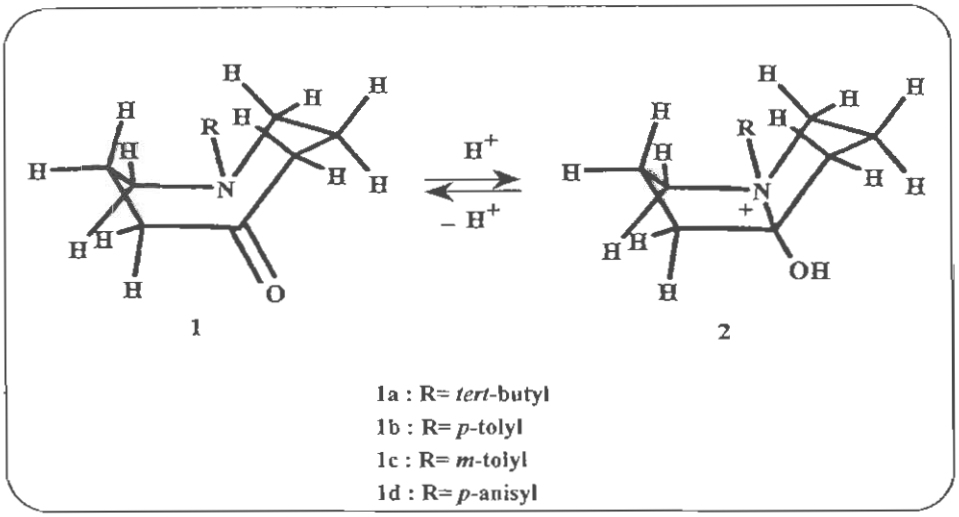

Fig. 1: Boat-chair conformation of N-substituted-5-azocanone derivatives in equilibrium with the bicyclic protonated form

show that ionization potential of oxygen lone pair ($n_{(O)}$) provides the best parameter for studying the interaction of the two functional groups, as it shows a homogeneous energy variation with distance between the functional groups [4]. In the present study, different semiempirical quantum mechanics methods have been used to evaluate the reliability of these methods for reproducing the extent of transannular interaction. UV spectroscopy has also been used to study the transannular interaction in a number of synthesized compounds.

RESULTS AND DISCUSSION

The homoconjugation in aminoketones has been interpreted as transannular amide resonance which leads to atypical chemical and physical properties of these compounds. Many medium ring aminoketones including several alkaloids have been studied in order to analyze transannular interactions [2,3]. In the series of cyclic aminoketones varying in ring size, the photoelectron spectroscopy indicates that the eight-membered ring system has the largest transannular interaction [6,7].

Molecular mechanics calculations[8,9] on N-aryl-5-azocanones show that the preferred conformation of the eight-membered ring is the boat-chair (BC) with the nitrogen and carbonyl group close together, Fig. 1. X-ray diffraction studies of N-*tert*-butyl (**1a**) and the N-*p*-tolyl (**1b**) azocanone derivatives show that the eight-membered ring adopts a boat-chair conformation with transannular N-->C_{CO} distance of 2.70 A° and 2.76 A° respectively [10,11]. A reliable quantum mechanics method should reproduce these distances. For these molecules performing a high level of *ab-initio* calculation is time consuming and costly; therefore the semiempirical Hamiltonians were employed to find out whether they reproduce the N-->C_{CO} distances in **1a** and **1b**. The results are given in Table 1. The AM1 Hamiltonian seems to be the best in reproducing the N-->C_{CO} distances compared with the experimental ones. Thus AM1 is the method of choice for studying the transannular interaction.

Table 1: N-->C_{CO} distances (in Angstrom) in N-tert-butyl-5-azocanone (1a) and N-(p-tolyl)-5-azocanone (1b), comparision of X-ray crystallographic data with theoretical ones.

Method	**1a**(Å)	**1b**(Å)
X-ray crystallography	2.70	2.76
AM1	2.86	2.85
PM3	2.97	2.98
MNDO	3.02	3.02
MINDO/3	3.36	3.37

Some parameters such as nitrogen charge density, oxygen charge density, oxygen lone pair ionization potential $n_{(O)}$ and the energy gap of HOMO and LUMO were computed by changing the aryl substituent, and cor-

relation between these parameters and Hammett substituent constants were checked. Among the mentioned variables only the plot of $n_{(O)}$ versus Hammett substituent constants (σ) shows a linear correlation, Fig. 2.

Synthesis of some compounds listed in the theoretical work was tried. While it was possible to, synthesize the 1-tolyl and 1-anisyl derivatives of 5-azocanone[12], the synthesis of precursors for other derivatives failed.

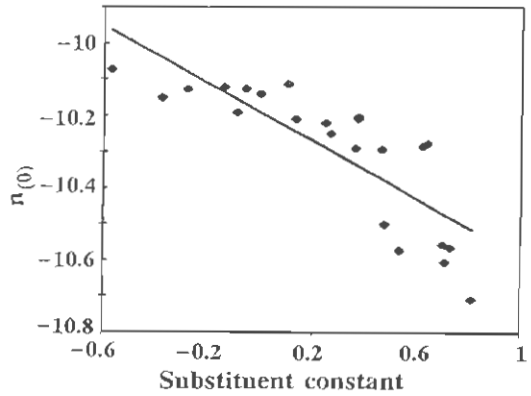

Fig. 2: Plot of $n_{(O)}$ versus Hammett substituent constants (σ) for 1-aryl-5-azocanones

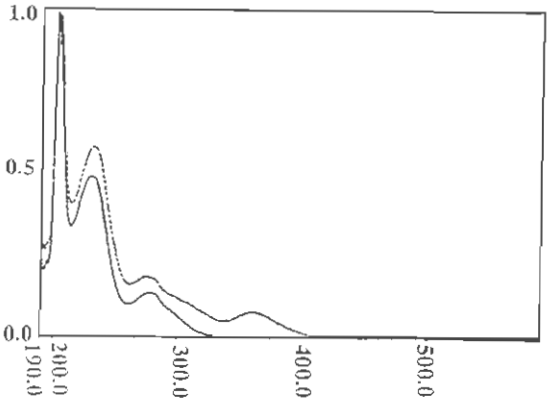

Fig. 3: Influence of concentrated hydrochloric acid on UV spectrum of cyclooctanone in methanol (— cyclooctanone,---- cyclooctanone + HCl)

The transannular interaction in the synthesized compounds were studied by UV spectroscopy. The UV spectrum of cyclooctanone shows one $n\rightarrow\pi^*$ transition centered at λ_{max} =278 nm which does not show any significant change when treated by concentrated hydrochloric acid, Fig. 3. The UV spectra of the N-*p*-tolyl (**1b**), 1-*m*-tolyl (**1c**) and N-*p*-anisyl (**1d**) compounds show two absorbtion bands tentatively assigned to the carbonyl $n\rightarrow\pi^*$ (270 nm) and the nitrogen lone pair to aromatic π^* (310 nm), Fig. 4. Both bands decrease by gradual addition of small amounts of hydrochloric acid, indicating the formation of the bicyclic form **2** in equilibrium with the parent compound, Fig. 1.

In conclusion, this study shows that AM1 Hamiltonian is the best among the semiempirical quantum mechanical methods for studying the transannular effects. The UV spectroscopy confirms the formation of transannular bond upon addition of trace amounts of acid, the protonated form being in equilibrium with the parent aminoketone.

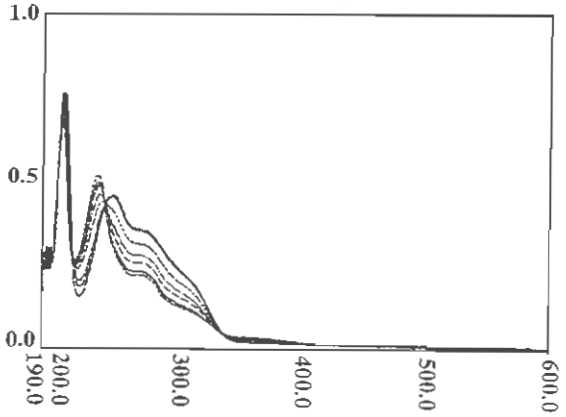

Fig. 4: Influence of gradual increase in concentration of hydrochloric acid on 1b in methanol (— without added acid, ---- with gradual addition of 10 μL., 0.5 N HCl)

CALCULATIONS

The initial structures were optimized by MMX force field implemented in PCMODEL software [13]. The AM1 [14], MNDO [15], PM3 [16] and MINDO/3 [17] calculations were run on an IBM PC by using MOPAC 6.0 [18] program.

EXPERIMENTAL

Shimadzu UV-Vis spectrophotometer was used for recording the UV spectra. Compounds were synthesized according to the published procedure [12]. Reagents were received from Merck and used without furthur purification.

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