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AROMATICITY AND CHEMICAL REACTIVITY IN ISOINDOLE[1]

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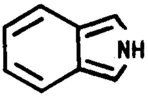
The chemical instability of isoindole (1) is well documented[2] and impeded its isolation and detailed characterization for nearly eighty years, until 1972, when it was reported by Bonnett and Brown[3], and later by Bornstein, Remy and Shields.[4] This ortho-quinonoidal nitrogen heterocycle is thermally unstable, reacts with atmospheric oxygen and undergoes Diels-Alder reactions in the pyrrole ring with dienophiles such as N-phenylmaleimide to yield bicyclic adducts (3).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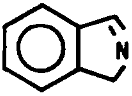
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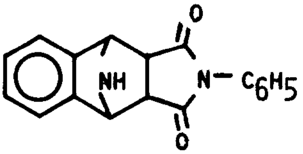

The great reactivity of isoindole contrasts sharply with the predictions of theoretical calculations, performed at various levels of sophistication, all of which indicate the molecule to be aromatic.[5] In view of the historical connection between aromaticity and diminished chemical reactivity, the potential coexistence in isoindole of both aromaticity and chemical instability seemed to us to present an apparent inconsistency which invited resolution. Accordingly, we undertook a spectral investigation of isoindole whose aims were to provide evidence for or against its aromaticity, and to characterize its electronic ground state, in order thereby to clarify the source of its reactivity. On the basis of our results, we propose herein a structural representation capable of accounting for both properties.[6]

Isoindole can be produced pure, in nearly quantitative yields, by flash vacuum pyrolysis.[4,7] Passage of 7-azabenzonorbornene through an unpacked quartz tube at 600° affords isoindole and ethylene; the latter is easily removed by fractional vaporization effected by replacement of the trap coolant, liquid nitrogen, with Dry Ice-acetone. It had been noted earlier[8] that this pyrolysis afforded a mixture of two isomers: isoindole (1, characterized by a broad NH absorption at ~δ 10 and a two-proton doublet at δ7.1 assigned to the protons adjacent to nitrogen), and isoindolenine (2, characterized by a one-proton triplet (J = 3Hz) at δ8.65 and a two-proton benzylic doublet (J = 3Hz) at δ4.87, suggesting the existence of an isoindole-isoindolenine equilibrium. Spectral evidence for such equilibria in the stable 1-phenylisoindole and two para-substituted derivatives was produced in 1964 by Veber and Lwowski[9]. They found that at room temperature there exists a mobile equilibrium whose position is markedly dependent upon the nature of the substituent and the solvent polarity.

That the product mixture resulting from the pyrolysis of 7-azabenzonorbornene was not an equilibrium mixture was clear from our observation that both its UV and NMR spectra were time-dependent. Thus, when the product mixture was dissolved in n-heptane at 25° C, the absorbance at 320 nm, due to isoindole, increased with time, following first-order kinetics ($t_{½}$ = 16 min), suggesting an adjustment of the product composition.

The equilibration process was investigated in more detail by NMR spectroscopy[10] in three solvents of widely differing polarities: toluene-d_8 (ϵ = 2.4), acetone-d_6 (ϵ = 20.7) and acetonitrile-d_3(ϵ = 37.5). In all cases at -40° C, the equilibration process was directly observable: peaks due to isoindolenine decreased in intensity with time and ultimately disappeared, while isoindole peaks increased. Eventually no isoindolenine was detectable.

The extent of the system's energetic preference for isoindole is underscored by the results of deuterium exchange experiments. Addition of D_2O to a solution of isoindole in acetonitrile-d_3 at either room temperature or -40° C resulted in instantaneous deuteration of the NH proton, as evidenced by the disappearance of its resonance and loss of the coupling between it and the adjacent protons. However, even on prolonged standing (30 - 60 minutes at room temperature), we found no incorporation of deuterium into the latter positions. In contrast, analogous experiments at room temperature carried out by us on 1-phenylisoindoles revealed deuteration of both NH and 3-positions to be instantaneous, complete and reversible, whereas at -40°, results duplicated those found for the parent isoindole. These findings demonstrate α-deuteriation to occur via the isoindolenine tautomer as an intermediate and imply a negligible amount of isoindolenine to be present in equilibrium with the parent heterocycle.

Since the energy difference between 1 and 2 should arise largely from the difference between their respective π-electron energies, and since 2 is an aromatic Schiff base, with a resonance energy appropriate thereto, our observations demonstrate isoindole to have a resonance stabilization energy greater than that of the aromatic isoindolenine, and thus, to be aromatic in accordance with theoretical predictions.[5,6]

To define the electron distribution in the ground state of isoindole, we analyzed its NMR spectrum, which in acetonitrile-d_3 consists of four well-defined regions: a broad, barely perceptible NH absorption at low field (ca.δ10.4); the protons H-1 and H-3 at δ7.16, split into a doublet due to coupling with the NH proton and further broadened by inter-ring couplings; and the protons of the carbocyclic ring, H-4, H-7 and H-5, H-6 which appear respectively at lower (δ7.5) and higher (δ6.8) field and give rise to an AA'BB' subspectrum.

Further splitting in the lower-field half of the AA'BB' spectrum (protons H-4 and H-7) arises from inter-ring coupling, probably between proton pairs 1,4 and 3,7.[11] Iterative analysis of the AA'BB' subspectrum using the computer program LAOCN3[13] gave the coupling constants shown in Table 1. Comparison of these values with the couplings of naphthalene[14] (taken to be a model for a fully delocalized, aromatic π-system) and 1,3-cyclohexadiene[14] (taken as a model for a classical, nonaromatic π-system) suggest the electron distribution in the carbocyclic ring of isoindole to lie between the two extremes, but much closer to that in naphthalene. However, the ratio of the vicinal coupling constants,[15] J_{56}/J_{45}, is significantly lower in isoindole (0.74) than in either naphthalene (0.82)[14] or indole (0.90)[16], indicating a slightly greater degree of bond fixation in the carbocyclic ring of isoindole

Table 1. Coupling Constants in Isoindole, 1,3-Cyclohexadiene and Naphthalene

Coupling[a]	1,3-Cyclohexadiene[b]	Isoindole[c]	Naphthalene[b]
J_{12}	9.64	8.49	8.30
J_{23}	5.04	6.29	6.83
$J_{13}(=J_{24})$	1.02	0.89	1.20
J_{14}	1.12	0.98	0.74
J_{23}/J_{12}	0.52	0.74	0.82

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[a] To facilitate comparison among different molecules, the numbering convention used here is that of a 1,3-butadiene.

[b] Reference 14.

[c] This work.

than in either of the latter compounds. This suggested to us that the properties of isoindole might profitably be understood in terms of the interaction between pyrrole and butadiene π-systems, an idea supported by our analysis of calculations of Dewar et al.[5c]

Annelation of butadiene to the 2,3 and 3,4 positions of pyrrole, respectively, yields indole and isoindole. Since the Dewar resonance energy (DRE) of butadiene is zero,[17] the difference between the DRE's of indole or isoindole and that of pyrrole is a measure of the stabilization deriving from interaction between the π-systems (the "annelation energy"). Whereas the annelation energy for indole (15.4 kcal/mole) compares favorably with the DRE of benzene (20 kcal/mole)[17], consistent with formation of a second aromatic ring, the annelation energy for isoindole is only 3.2 kcal/mole, suggesting either that its aromaticity derives primarily from one ring, or that it is in fact a ten π-electron aromatic system whose low resonance energy is reflected in some bond alternation throughout the π-system. The calculated bond lengths[5c] for the pyrrole ring of isoindole are essentially equal to those of pyrrole itself, while the bond lengths in the carbocyclic ring are the same as those of polyene single and double bonds. Our NMR data, on the other hand, seem more consistent with the latter possibility.

Either representation, however, reconciles the aromaticity of 1 and its reactivity toward dienophiles. Dienophile attack at C-1 and C-3 reduces the contribution of the pyrrole ring to the stability of the π-system while resulting in the simultaneous formation of a benzene ring. Thus, the endothermic contribution to the activation energy due to disruption of the π-system (isoindole or pyrrole, depending on the model chosen) is offset by an exothermic contribution due to formation of the benzene ring, leading to a low activation energy, rendering isoindole hyperreactive in the pyrrole ring, as observed experimentally.

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