

Computational Analysis of Isoindole-Based Reagents for Guanidinylation

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2*H*-Isoindoles are highly reactive heterocyclic intermediates of theoretical and practical interest and are widely used as building blocks in organic and pharmaceutical synthesis [1]. Although isoindoles possess an aromatic π -system, the position of the nitrogen atom prevents the formation of a Clar aromatic sextet in any six-membered ring, resulting in enhanced reactivity relative to indole isomers. Their cycloaddition reactivity is driven by restoration of aromaticity in the fused aryl system, and it is comparable to that of isoacenofurans, which are isoelectronic with the iso[aceno]indoles discussed here [2].

The cycloaddition reactivity of *N*-amidino benzannulated isoindoles was studied experimentally and computationally using DFT at the M06-2X/6-311+G(d,p) level. Linear homologation significantly increases reactivity, which is attributed to the intrinsic instability of the isoindole framework and energetic stabilization upon re-aromatization in cycloadducts.

Two homologated derivatives, 2*H*-benzo[*f*]isoindole and 2*H*-naphtho[2,3-*f*]isoindole, were synthesized *via* multistep routes. Their cycloaddition reactivity toward dienophiles was evaluated, and pronounced instability in solution was confirmed.

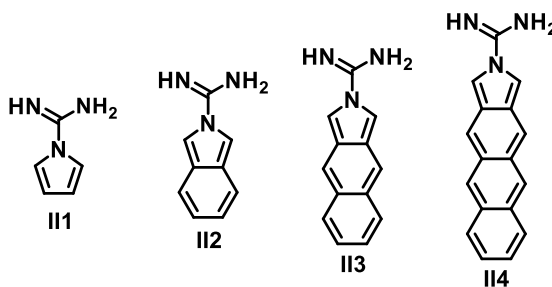


Figure 1. Isoindole linear homologs II1–II4 used in computational analysis

References:

- [1] T. J. Donohoe, in E. J. Thomas (ed.), *Science of Synthesis, 10: Category 2, Heteroarenes and Related Ring Systems*, Thieme, Stuttgart, **2001**, pp. 653-692.
- [2] E. Clar, *The Aromatic Sextet*, Wiley, New York, NY, **1972**.