

## Controlling the Conformation of 2-Dimethylaminobiphenyls by Transient Intramolecular Hydrogen Bonding

D. Del Giudice, M. Valentini, C. Sappino, E. Spatola, A. Murru, G. Ercolani, S. Di Stefano, *J. Org. Chem.* **2023**, *88*, 7, 4379–4386

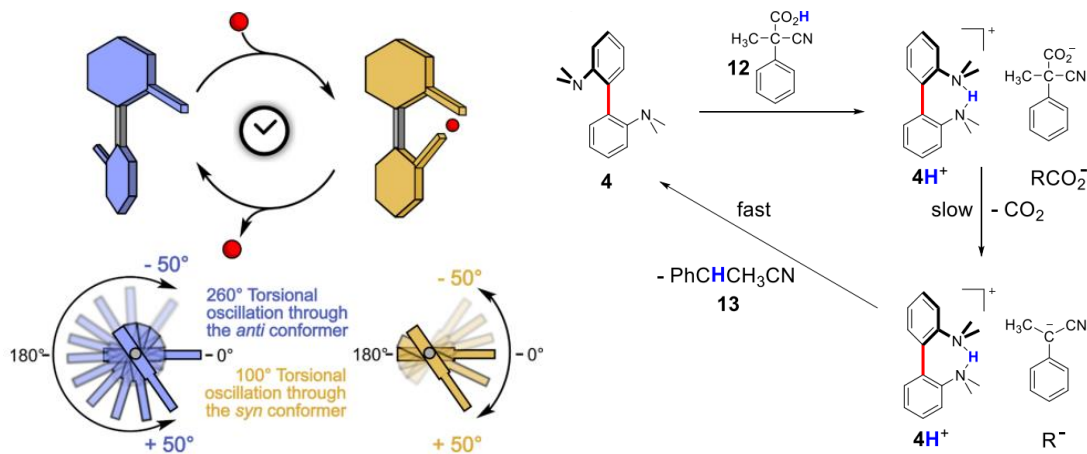


Fig 1: Graphical illustration of conformational controlled 2-Dimethylaminobiphenyls by transient intramolecular hydrogen bonding

### Who are the corresponding authors and what are their research areas?

Stefano Di Stefano – Full Professor of Organic Chemistry at the University of Rome La Sapienza, Italy

He is working in the field of physical organic chemistry and his research interest is focused on the synthesis and development of supramolecular catalysts. Main ongoing study of Prof. Stefano is involving the controlled dynamic chemical systems.

Gianfranco Ercolani – Full Professor of Organic Chemistry at the University of Rome Tor Vergata, Italy

He is a supramolecular chemist focusing on self-assembly, mechanisms of cooperativity and asymmetric catalysis.

### What is the main claim of the article?

The conformational mobility of the acid-base operation-based biphenyl systems can be temporally controlled or restricted by using an activated carboxylic acid (2-cyano-2-phenylpropanoic acid, **12**) as a chemical fuel. The addition of fuel protonates the pendant amino group that forms the conformationally restricted state due to the formation of a hydrogen bond. Moreover, the fuel conjugate base is capable to smoothly decarboxylate under basic conditions and act as a strong base, so the addition of the fuel not only plays a role as a proton donor but also drives the system out of the equilibrium to the conformationally mobile state by back proton transfer process facilitated by the strong base formed after decarboxylation (**R<sup>-</sup>**) (Fig.1)

### How is it demonstrated?

Kinetic studies have been elaborated by the authors by monitoring the reaction progress over time the decarboxylation of the fuel. The chemical shift of methyl substituent was used to follow the conversion of protonated specie (conformationally restricted state) to the initial neutral specie (conformationally mobile state) (Fig.2).

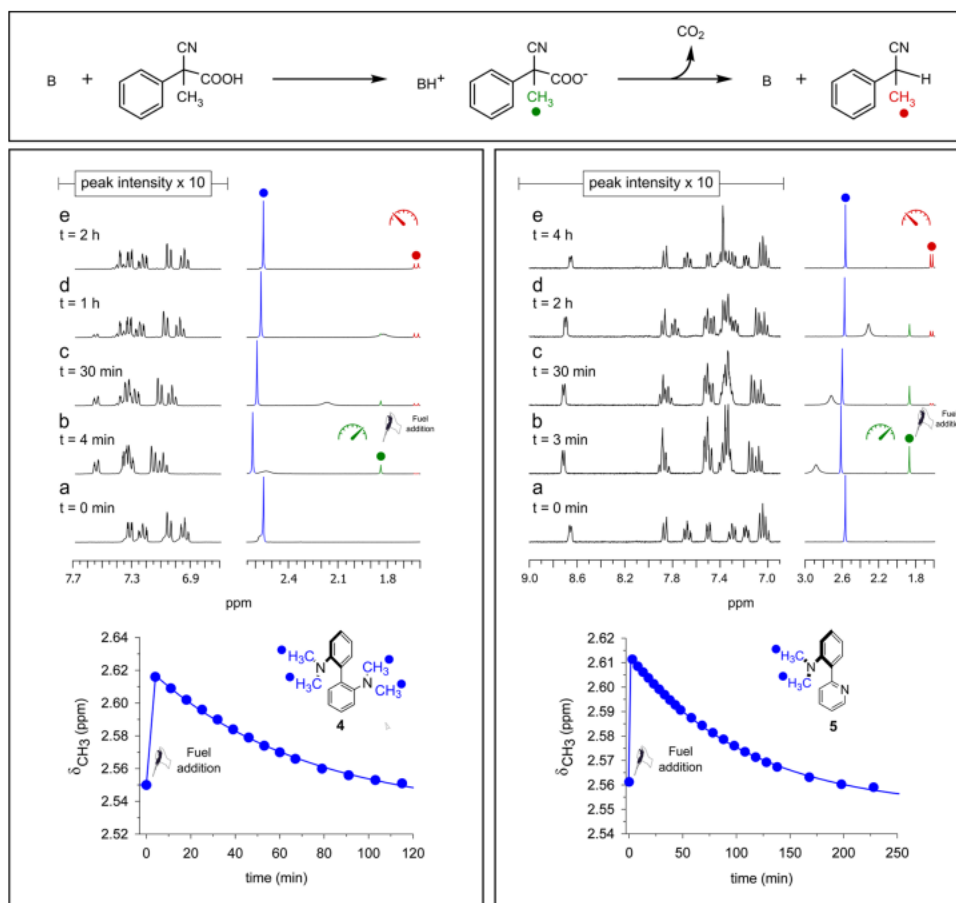


Figure 2.  $^1\text{H}$  NMR monitoring and corresponding kinetic traces (first-order kinetic fit) for reactions of 5.0 mM 12 with 5.0 mM 4 (left panel) and 5.0 mM 5 (right panel). Blue singlet belongs to the four methyl groups of 4 in the left panel and to the two methyl groups of 5 in the right panel. The green singlet (both left and right panels) belongs to the methyl group of the carboxylate anion, and the red doublet (both left and right panels) to the methyl group of waste product 13.

Authors also support their claim on fuel-driven conformational restrictions by showing more insight DFT calculation experiments. Potential energy curves of 4/4H<sup>+</sup> and 5/5H<sup>+</sup> as a function of the torsional angle around the central C–C bond were presented. Large amplitude torsional oscillation spanning of neutral species passing through *anti* conformation and more restricted oscillation spanning of protonated species through *syn* conformation are apparently supported by the results in Figure 3.

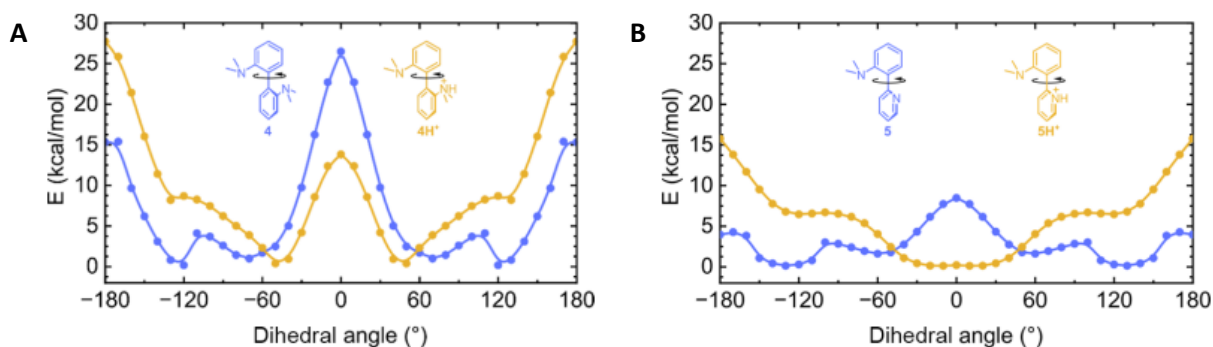


Figure 3. **A)** Potential energy curves of 4 (sky blue) and 4H<sup>+</sup> (light brown) as a function of the torsional angle around the central C–C bond calculated with the  $\omega\text{B97XD/6-31+G(d,p)/SMD}(\text{CH}_2\text{Cl}_2)$  method. Energies in kcal/mol are relative to the fully optimized structure of the corresponding global minimum. The zero dihedral angle corresponds to the *syn* conformation. **B)** Potential energy curves of 5 (sky blue) and 5H<sup>+</sup> (light brown) as a function of the torsional angle around the central C–C bond calculated with the  $\omega\text{B97XD/6-31+G(d,p)/SMD}(\text{CH}_2\text{Cl}_2)$  method. Energies in kcal/mol are relative to the fully optimized structure of the corresponding global minimum. The zero dihedral angle corresponds to the *syn* conformation.

Additionally, NOESY experiments are performed to show evidently the presence the NOESY contact between methyl proton  $H_i$  and proton  $H_a$  before protonation. After addition of fuel, the previously mentioned contact disappears. it was replaced by a weak visible  $H_a$ - $H_e$  NOESY contact as a consequence of the conformational change. (Fig. 4)

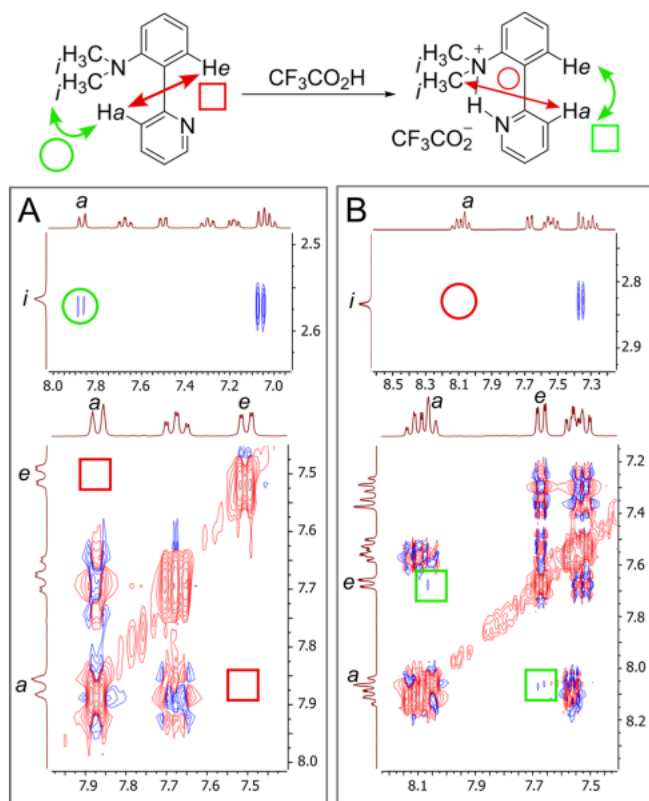


Figure 4. Diagnostic portions of **5** (A) and  $5H^+$  (B) NOESY spectra. From spectrum A, it is evident the presence of the NOESY contact between methyl protons  $H_i$  and proton  $H_a$  and the absence of any NOESY contact between protons  $H_a$  and  $H_e$ . The opposite holds in the case of spectrum B related to  $5H^+$

### What are the typical experimental conditions?

**Kinetic studies:**  $^1H$  NMR monitoring reactions (5.0 mM 2- cyano-2-phenylpropanoic acid with 5.0 mM of ditopic base (4 or 5) in  $CD_2Cl_2$  at 25 °C.) -

**DFT calculation:** Potential energy curves are calculated with the  $\omega B97XD/6-31+G(d,p)/SMD(CH_2Cl_2)$  method.

### Which are the key related papers?

1. J. A. Berrocal, C. Biagini, L. Mandolini, S. D. Stefano, *Angew. Chem., Int. Ed.* **2016**, *55*, 6997– 7001.