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Long-Range Bonding/Nonbonding Interactions: A Donor−Acceptor Resonance Studied by Dynamic NMR

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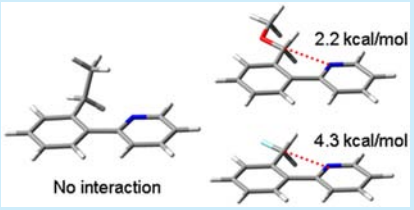
Supporting Information

ABSTRACT: Long-range bonding interactions were evaluated using variable-temperature NMR spectroscopy and suitable 2′-CH_2X-substituted phenylpyridines (X = Me, NMe_2, OMe, F). It was found that the arylpyridyl rotational barriers were lower when electronegative atoms were bound to the α carbon of the 2′ moiety. This effect was ascribed to a stabilizing interaction in the transition state due to the lone pair of the heterocyclic nitrogen with the α carbon. Computational support for this hypothesis came from CCSD(T)/6-31+G(d) calculations. Steric effects of the X moiety were ruled out by comparison of the rotational barriers of analogous biphenyls.



Weak chemical interactions play a key role in chemistry. They are essential for biological systems and they can be employed to design supramolecular assembly and scaffolds.[1] Among them, van der Waals dispersive forces,[2] hydrogen bonds,[3] halogen−halogen,[4] and $\pi-\pi$ interactions[5] are the most studied, and others have been under investigation in the recent past.[6]

During our dynamic NMR studies of 2-(2′-alkylphenyl)-pyridines,[7] we came across an apparent discrepancy. While the CH_2 signal of 2-(2-ethylphenyl)pyridine (**1**) (Table 1) did show decoalescence below −164 °C ($\Delta G^{\ddagger}$ = 5.9 kcal/mol), in the case of 2-[2-(methoxymethyl)phenyl]pyridine **3** the coalescence point was not observed at temperatures as low as −173 °C (Figure 1). This means the barrier was too small to allow experimental determination by dynamic NMR measurements.[8,9] In order to obtain additional data, we prepared the dimethylamino analogue **4**. When cooled to −170 °C, compound **4** did show splitting of the CH_2 signal (Figure S1, Supporting Information, SI) with a lower experimental aryl−aryl rotational barrier (4.8 kcal/mol).

Table 1. Experimental and Calculated Torsional Barriers for 2-Arylpyridines[a]

compd	X	exptl value	planar TS	skewed TS	ΔE pl-sk[b]
1	Me	5.9[c]	8.4	**6.2**	+2.2
2	H		5.9[d]	5.9[d]	0[d]
3	OMe		**4.9**	6.7	−1.8
4	NMe_2	4.8	6.8	**6.6**	+0.2
5	F		**4.0**	6.9	−2.9

[a]Calculations at the CCSD(T)/6-31+G(d)//ωB97XD/6-31G(d) level (energies in kcal/mol). Values in bold indicate the preferred transition state. [b]A positive value indicates a more stable skewed TS. [c]See ref 7. [d]For this compound there is only one TS.

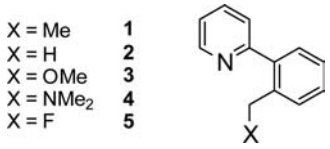


Figure 1. Model compounds for computational studies.

Common sense suggests that the methoxymethyl group should be bigger than a methyl group because the methoxy entity requires more space than a single hydrogen atom. Such plausible expectations are corroborated by all standard criteria assessing steric effects. Charton's "effective" upsilon parameters,[10] derived from van der Waals radii, place methoxymethyl (υ = 0.63) above methyl (υ = 0.52) and even between ethyl (υ = 0.56) and propyl (υ = 0.68). Winstein's *A* values[11] based on the free energy differences between axially substituted cyclohexanes and their equatorial invertomers rank methoxymethyl (*A* = 1.72) at the same level as methyl (*A* = 1.74). Finally, our *B* scale based on biphenyls torsional barriers[12] puts methoxymethyl (*B* = 8.6) *ex aequo* with ethyl (*B* = 8.7) and on top of methyl (*B* = 7.4).

All the more disconcerting it was to find this sound order of bulkiness reversed when we turned from 2-alkylbiphenyls to 2-(2′-alkylphenyl)pyridines.

To find a possible explanation, we resorted to quantum chemical calculations. The geometries of the stationary points on the aryl−aryl rotation pathway of **1** and **3** were optimized at the ωB97XD/6-31G(d) level of theory. Two different transition

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states (TS) were modeled and optimized, one corresponding to a N−C_1−C_1'−C_2' dihedral angle of 180° and the other with the dihedral set to 0°. The two TS were validated by frequency analysis, showing a single imaginary frequency corresponding to the rotation around the aryl−aryl bond. In both cases, the lower energy transition state corresponds to the crossing of the CH_2X group on the side of the pyridine nitrogen (i.e., N−C_1−C_1'−C_2' ≈ 0°). This is conceivable because of the smaller steric interference of the lone pair of nitrogen with respect to an hydrogen atom when the angle is ∼180°.[7] Once the aryl−aryl torsional angle of the TS was modeled, two different dispositions of the CH_2−X moiety are available. The first puts the X fragment in the same plane of phenyl and pyridine ("planar" conformation), while the second has the X fragment out of the plane ("skewed" conformation). Both of the geometries were optimized and validated as transition states by frequency analysis and IRC calculations (see the SI). It was found that the energy barrier for compound **3** (X = OMe) was smaller than that of **1** and **2**, while the barrier calculated for the *N*,*N*-dimethylamino compound **4** was in the middle. However, we noted that the calculated energy barriers were lower than the experimental ones (see Table S1, SI, for a summary). This outcome could be due to a wrong estimation of the contribution of the pyridine lone pair in the transition state.[13] For this reason, we calculated the single-point energies at the CCSD(T)/6-31+G(d)//ωB97XD/6-31G(d) level (Table 1).

The calculated value for the rotational barrier of 2-(2-ethylphenyl)pyridine (**1**) benchmarked the reliability of these calculations. Nevertheless, at the CCSD(T) level of theory the activation energy for aryl−aryl rotation of **3** was again found to be *smaller* than that of **1** and **2** (Table 1). A close examination of the transition-state geometries showed that the conformation assumed by the ethyl group in the best TS is substantially different from that of methoxymethyl. In the first compound, the methyl group has a dihedral angle of 80° (Me−CH_2−C_2'−C_1') with the phenyl plane, whereas the same angle is exactly 180° for the CH_2OMe group (O−CH_2−C_2'−C_1' dihedral angle). When the alternative TS (i.e., the methyl at 180° and OMe at ∼75°) were calculated, their energies were higher than the previous ones by 2.2 and 1.8 kcal/mol (see Figure 2). This trend was confirmed by the calculation of the energy barrier to rotation of 2-(*o*-fluoromethylphenyl)pyridine **5**, where the calculated value was lower than that of **3** and **4** (Table 1). In the case of compound **4** the two transition states have roughly the same energy.

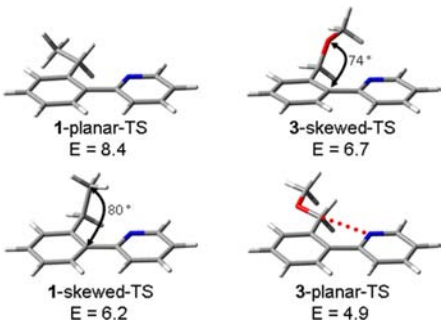

Figure 2. Two available transition states for aryl−aryl rotation of compounds **1** and **3**. Energies (in kcal/mol) were calculated at the CCSD(T)/6-31+G(d)//ωB97XD/6-31G(d) level, and they are relative to the ground states.

The reversed preference in the TS geometry of **3** with respect to **1** can be rationalized by considering a stabilizing interaction by the lone pair of the nitrogen that lowers the TS energy of compounds **3**−**5**. As long as the nitrogen atom disposes of its free doublet it may share it with a neighboring electron-deficient center, provided the correct geometry is achieved. Such kind of assistance is at the basis of anomeric effects[14] and neighboring group participations[15] if the nitrogen donor site and the halide (or alkoxy) acceptor site are part of geminal or vicinal bonding patterns. What makes unique the situation met with α-hetero-substituted 2-arylpyridines is the distance between the heterocyclic nitrogen atom and the α-carbon, the two centers being separated by four interposed bonds with no conjugative effects. Moreover, the amplitude of the barrier-lowering donor−acceptor interaction is modulated by the nature of the heteroelement.

In this framework, the long-range interaction manifests itself as a resonance of bonding and nonbonding limiting structures (**A** and **B** in Figure 3). For reasons of proximity, only the coplanar transition state of the torsional motion can benefit from this electron-density leveling interaction.

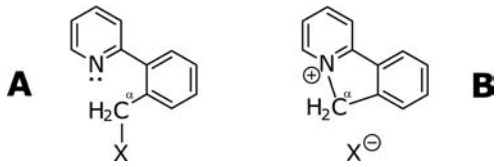

Figure 3. Two limiting structures for the long-range interaction.

The resonance extending from the pyridine nitrogen through the benzylic α-carbon to the heterosubstituent X is accompanied by a respectable gain of energy. If we assume that all 2′-CH_2X substituents exert the same steric hindrance (see below for the experimental confirmation), the nonclassical long-range interaction lowers the torsional barriers at an extent corresponding to the stabilization of the transition state, where this interaction can be effective (Figure 4).[16]

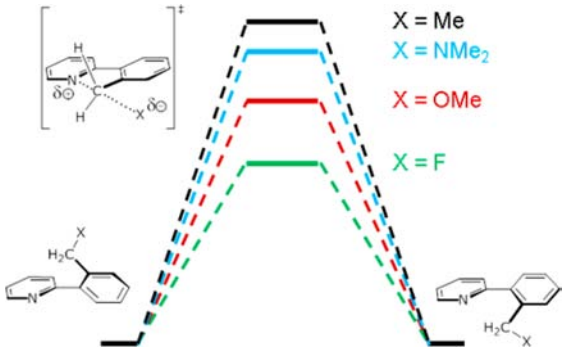

Figure 4. Schematic representation of the stabilizing interaction.

Although there was no reason to doubt the validity of the CCSD(T) computational results, we strived for further experimental confirmation. To make the torsional barrier more suited to the dynamic-NMR technique,[17] a methyl group was installed in the 3-position of the pyridine ring (compounds **6**−**10** of Table 2).

For convenience of synthesis, the model compounds **6**−**8** were prepared from 3,5-dimethylpyridine by a Ziegler-type addition[18] of 2-ethylphenyllithium, [2-(dimethylamino)methyl]-

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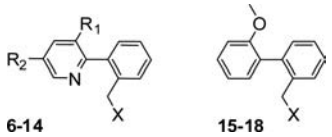
Table 2. Experimental and Calculated Torsional Barriers for Compounds 6−18[a]



6-14 15-18

compd	R_1	R_2	X	exptl barrier	calcd barrier	ΔE pl-sk[b]
6	Me	Me	Me	13.1	13.1	2.3
7	Me	Me	NMe_2	12.8	14.7	0.0
8	Me	Me	OMe	11.1	12.4	−1.4
9	Me	H	OMe	10.9	12.2	−1.4
10	Me	H	F	8.8	10.5	−3.4
11	Et	Et	H	13.7		
12	Et	Et	Me	14.4		
13	Et	Et	NMe_2	14.7		
14	Et	Et	OMe	12.6		
15			Me	15.9	18.9	2.1
16			NMe_2	15.5	18.8	3.1
17			OMe	15.1	17.7	2.4
18			F	15.1	17.9	1.5

[a]Calculations at the CCSD(T)/6-31+G(d)//ωB97XD/6-31G(d) level (energies in kcal/mol). [b]A positive value indicates a more stable skewed TS.

phenyllithium and (2-(methoxymethyl)phenyl)lithium,[19] followed by spontaneous lithium hydride elimination at ambient temperature. Compound **10** (X = F) could not be prepared this way because the intramolecular nucleophilic attack by the lithium amide intermediate at the fluorinated benzylic carbon led to the cyclized product (see below). Nevertheless, compound **10** was obtained by Suzuki−Miyaura cross-coupling between 2-bromo-3-methylpyridine and [(2-(fluoromethyl)phenyl]boronic acid. To check whether the presence of the 5-methyl group on the pyridine ring could modify the TS geometry and the rotational barrier by inductive electronic effect we prepared compound **9**. As proven by the identity of the rotational barriers of compounds **8** and **9**, the methyl in position 5 of pyridine has no effect on the torsional barrier.

An evaluation of the contribution of hydrogen (X = H) was also desirable, but 2′,3,5-trimethyl-2-phenylpyridine lacks diastereotopic nuclei and is hence unsuitable. To fill this gap, another set of compounds (**11**−**14**, Table 2) was prepared by adding the suitable aryllithium onto the 2-position of 3,5-diethylpyridine followed by thermal rearomatization.

All of the torsional barriers were derived by line-shape simulation of the signal of CH_2X that splits into an AB system when the aryl−aryl rotation is slow on the NMR time scale. Spectra were acquired in CD_2Cl_2 or in $CDFCl_2$ at a field of 14.4 T (600 MHz for ^1H, see Figures S2−S14, SI, for the spectra and simulations at different temperatures).

The results collected in Table 2 convey an unequivocal message. Electronegative substituents such as oxygen and fluorine substantially lower the activation energy for the rotation around the aryl-pyridyl axis, while the effect of a methyl instead of an hydrogen has a tiny effect on the barrier (compound **11** vs **12**). The effect of the nitrogen substitution on the α carbon is less straightforward (compound **6** vs **7** and **12** vs **13**). In these cases, the lone pair of the sp^3 nitrogen is highly nucleophilic, and it can be oriented in the ground state in such a way to develop a stabilizing interaction with the electron-poor carbon in position 2 of pyridine.

For all of the compounds containing heteroatoms in the α position, the calculated transition states showed that the X group is coplanar with the phenyl ring and points away from the nitrogen of pyridine. As discussed above, this geometry has the correct disposition of the two partners for the interaction of the nitrogen lone pair with the LUMO of C−X. On the contrary, the lowest energy TS in compounds **6**, **11**, and **12** was always the skewed one. When the energy difference between the planar TS and the skewed TS is evaluated (Table 2), the stabilization of the planar TS regularly increases with the leaving group ability.

In addition, the results obtained when trying to prepare the compound bearing a 2′-CH_2Br group can be discussed within this framework. The reaction of 2-bromobenzyl bromide with 2-pyridineboronic acid led to prompt cyclization to 6*H*-pyrido[2,1-*a*]isoindol-5-inium bromide (**B** structure of Figure 3). The same result was found also when [2-(bromomethyl)phenyl]boronic acid was reacted with 2-bromopyridine or when 2-[2-(hydroxymethyl)phenyl]-3-methylpyridine was treated with CBr_4 in the Appel conditions.[20] The same outcome was obtained in the attempt to prepare the 2′-CH_2Cl compound by the same synthetic approaches. All of these results are in agreement with a strong interaction of the pyridine lone pair with the benzylic carbon, leading to cyclization in the presence of a better leaving group such as chloride or bromide.

The key role played by the pyridine lone pair in the stabilization of the coplanar transition state can be further confirmed by comparing the rotational barriers of the analogous biphenyls **15**−**18** where a methoxy group was installed in the *ortho* position to tune the aryl−aryl rotational barriers to values similar to those of compounds **6**−**10**.[21] Calculations suggested that in this series of compounds the rotational barrier were very similar on varying the X substituent. Between the two feasible transition states, the preferred one corresponds to a $C_2-C_1-C_1'-C_2'$ dihedral angle close to 180°, where the steric interaction between the 2-methoxy and 2′-CH_2X moieties is minimized. Within this series of compounds, the preferred conformation of the CH_2X group in the best transition state was always the skewed one. Biphenyls **15**−**18** were easily prepared by Suzuki−Miyaura coupling (see the SI for details), and the experimental rotational barriers were indeed found to be clustered in a very limited range (less than 1 kcal/mol, see Table 2), thus confirming that all of the CH_2X groups have almost identical steric contributions.

The long-range effect described above evokes short-range "nonclassical" electronic interactions such as "negative hyperconjugation"[22] and homoaromaticity.[23] We further recognize a close relationship to the Dunitz−Bürgi trajectory continuum[24] and Mayr's nucleofugality parameters.[25] The concept of long-range resonance interactions raises new questions about intramolecular interactive effects, and further investigations are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic details, spectroscopic data, and variable-temperature NMR spectra for compounds **4** and **6**−**18**. ^1H and ^{13}C NMR spectra of compounds **4** and **6**−**18**. Computational details of compounds **1**−**10** and **15**−**18**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01152.

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Author Contributions

The manuscript was written through contributions of all authors

Notes

The authors declare no competing financial interest.
[‖]Deceased June 26th, 2013.

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(9) In the case of *o*-tolylpiridine, a diastereotopic probe had been installed on the 4-position of pyridine. See ref 7

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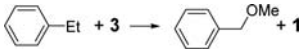
(16) In principle, ground-state effects due to the different X substituents cannot be excluded. However, this contribution was found to be negligible by the calculations of the following isodesmic reaction (see the SI for details).



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