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The anisotropic effect of functional groups in ^{1}H NMR spectra is the molecular response property of spatial NICS—the frozen conformational equilibria of 9-arylfluorenes

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Dedicated to Professor Ferenc Fülöp on the occasion of his 60th birthday

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ABSTRACT

Rotation about the single bond adjoining the aryl and fluorene moieties in 9-arylfluorenes can be frozen out on the NMR timescale if methyl groups are located at either one or both of the *ortho* positions of the aryl substituent. In the ground-state of these rotamers, the planes of the aryl and fluorene moieties are perpendicular to each other and the methyl substituents are consequently positioned either above the fluorene moiety or in-plane with it; thus, the methyl protons are either shielded or deshielded, respectively, due to the ring current effect of the fluorene moiety. This anisotropic effect on the ^{1}H chemical shifts of the methyl protons has been quantified on the basis of through-space NMR shieldings (TSNMRS) and subsequently $\Delta\delta_{calcd}$ compared with the experimentally observed chemical shift differences, $\Delta\delta_{exp}$. In this context, the experimental anisotropic effects of functional groups in the ^{1}H NMR have proven to quantitatively be the molecular response property of theoretical spatial nucleus independent chemical shieldings (NICS). Differences between $\Delta\delta_{calcd}$ and $\Delta\delta_{exp}$ were, for the first time, also quantified as arising from steric compression.

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1. Introduction

The spatial magnetic properties of molecules are able to be assessed by through-space NMR shieldings (TSNMRS) and visualized as iso-chemical-shielding surfaces (ICSS).[1] This methodology,[1] developed by us and successfully employed to depict and quantify the anisotropic effects or ring current effects of functional groups or aryl substituents on ^{1}H chemical shifts, has been employed for stereochemical assignments or to otherwise examine diastereomers as well as to ascertain the conformational preference of various structures.[2–14]

These anisotropic effects, however, evaluated with respect to their influence on the chemical shifts of proximate protons, are not isolated substituent effects on $\delta(^1H)$ but can often be accompanied by other structural influences, at the very least by 'steric compression' effects, which are of contrary influence chemical shift-wise. For example, the strong shielding experienced by a proton positioned above an aryl moiety is due to the ring current effect whilst any strong deshielding exhibited by such a proton is due to steric compression.[15,16] Often however, these competing effects may not be recognized leading to the formulation of incorrect conclusions. For example, the ^{1}H chemical shift difference between the axial and equatorial protons in cyclohexane is not due to the anisotropic effect of the C–C single bond[5] whilst the deshielding by 1.57 ppm of H-4 in 11-ethynylphenanthrene relative to its counterpart in phenanthrene is not due to the anisotropy of the C≡C triple bond.[8] Our approach[1] has allowed for the reappraisal of these more-than-prevalent assertions in various prescribed NMR textbooks.

Even if there are persistent and strong reservations[17] to qualifying the molecular response properties of experimentally proven anisotropic effects arising from functional or aromatic groups on the ^{1}H chemical shifts of proximate protons by unobservable quantities, such as nucleus independent chemical shielding (NICS),[18] our results can serve as definitive proof that TSNMRS (spatial NICS) not only successfully assign the configuration and diastereoisomerism of structures,[2–14] but also the conformational state if the underlying dynamic process is fast on the NMR timescale.[19] Thus TSNMRS visualize and quantify the anisotropic effects of functional groups in NMR spectra, which can be measured experimentally, and can thus be evaluated as the molecular response property of spatial NICS.[19]

We have for some time been looking for structures where the anisotropic or ring current effects of functional groups or aryl substituents on the chemical shifts in the ^{1}H NMR spectra can be

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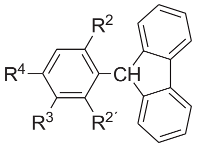
determined free of steric compression and other structural influences, and we appear to have found useful structures by way of the 9-arylfluorenes. In this system, the rotation about the single bond adjoining the aryl and fluorene moieties can be frozen out on the NMR timescale if methyl groups are located at either one or both of the *ortho* positions of the aryl substituent. In the ground-state of these rotamers, the methyl substituents are positioned either above the fluorene plane or in-plane with it and are expected to be exposed to the fluorene ring current effect in both instances. However, whilst in-plane, the methyl groups are expected to be almost free of steric compression or other structural influences. For this reason, the TSNMRS of five 9-(methyl)arylfluorenes **1**–**5** (Scheme 1) have been calculated by our standard methodology[1] and compared with the experimental chemical shifts of the methyl protons[20] in order to evaluate our assertion with the corresponding results presented herein.



No.	R2	R2´	R3	R4
1	CH_3	H	H	H
2	CH_3	CH_3	H	H
3	CH_3	CH_3	H	CH_3
4	H	H	CH_3	H
5	H	H	H	CH_3

Scheme 1.

2. Computational details

Quantum chemical calculations were performed using the Gaussian 03 program package.[21] The structures of **1**–**5** were fully optimized at the MP2/6-311G** level of theory[22] and NICS values[18] were computed for these geometries using the GIAO method[23] at the B3LYP/6-311G** theory level. To calculate the NICS values, ghost atoms were placed in a lattice of −10 Å to +10 Å with a step size of 0.5 Å in the three directions of the Cartesian coordinate system. The zero points of the coordinate system were positioned at the centers of the structures. The resulting 68,921 NICS values were analyzed and visualized using SYBYL 7.3 molecular modeling software.[24]

3. Results and discussion

The calculated structures were in concert with the assertions of Siddall and Stewart,[20] viz. in the ground-state conformers the planes of the aryl and fluorene moieties are perpendicular to each other and the methyl substituents are positioned either above the fluorene moiety or in-plane with it. Thus, the methyl protons should be either shielded or deshielded, respectively, subject to the ring current effect of the fluorene moiety (cf. Fig. 1 for compound **3**). The chemical shifts of the methyl protons in compounds **1**–**5**, taken from Siddall and Stewart,[20] are presented in Table 1. For compounds **1**–**3** with *ortho*-methyl groups, two resonances, one strongly shielded, the other slightly deshielded, were observed; in the case of **1**, two distinct conformers were also experimentally observed, and this observation was complemented by the ab initio calculations. For compounds **1**–**3**, the rotation about the bond linking the aryl and the fluorene moieties is slow on the NMR timescale due to the steric bulk of the methyl substituents. This is not the case in **4** and **5** where the *meta*- and *para*-methyl substituents are obviously too far away to hinder this dynamic process adequately; lowering the temperature of the sample in methylene chloride to −90 °C did not result in meaningful linewidth changes for these compounds.[20]

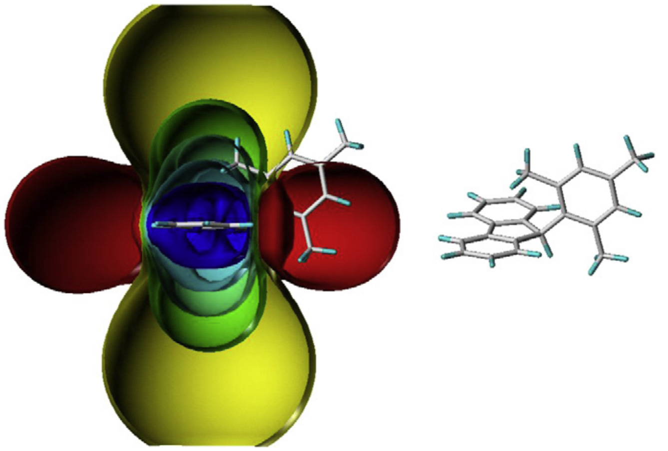


Fig. 1. Ground-state conformer of 9-arylfluorene **3** (right) and visualization of the magnetic properties (TSNMRS, left) of the fluorene moiety as ICSS of different direction and size (blue represents 5 ppm shielding, cyan 2 ppm shielding, greenblue 1 ppm shielding, green 0.5 ppm shielding, yellow 0.1 ppm shielding and red −0.1 ppm deshielding).

Only the *ortho*-methyl protons, evidently, are influenced by the anisotropy of the fluorene moiety with $\Delta\delta_{exp} \geq 1.5$ ppm being a strong indication of this. The *meta*- and *para*-methyl protons, by contrast, emphasize the typical chemical shifts for these kinds of protons by lying in the range 2.21–2.27 ppm and are obviously not sufficiently proximate to be influenced by the anisotropic effect of the fluorene moiety. On the other hand, these chemical shifts, especially those of the *para*-methyl protons, are useful references for the chemical shifts of the methyl protons in the aryl moiety free of the anisotropic effect of the fluorene moiety and $\Delta\delta_{exp}$ of the *ortho*-methyl protons can thus be assessed based on the anisotropic effect influences of the fluorene moiety. Since we consider anisotropic effects/ring current effects in ^{1}H NMR spectra as the molecular response property of spatial NICS (TSNMRS),[19] the TSNMRS of the fluorene moiety were calculated by our methodology[1] and the results (cf. Table 1) examined with respect to these aforementioned considerations.

Actually, $\Delta\delta_{exp}$ of the *ortho* and *para*-methyl protons of the mesityl groups in transition metal 1,2-diimine[25] and acetylacetonato chelates[26] have already been employed to serve as a sensor for chelatoaromaticity. Evidence for diamagnetic ring current effects, however, could not be provided.[25,26]

As concluded by Siddall and Stewart[20] for the preferred conformers of **1**–**3** (and also in **4** and **5**), the planes of the aryl and the fluorene moieties are perpendicular to each other (Table 2). In Fig. 1, the preferred conformer of **3** is depicted; analogous conformers with same or similar dihedral angle between the two molecule moieties (cf. Table 2) were obtained for the other compounds under study. Also depicted in Fig. 1 are the TSNMRS of the fluorene moiety. The distinct $\Delta\delta_{exp}$ between the *ortho*-methyl signals is immediately evident and comprehensible. The protons of the *ortho*-methyl group above the fluorene moiety are strongly shielded (positioned between shielding ICSS of +1 and +2 ppm), whilst those of the other *ortho*-methyl group are only modestly deshielded and are positioned between deshielding ICSS of −0.5 and −0.1 ppm. The *para*-methyl group is outside of the shielding (+0.1 ppm) and deshielding (−0.1 ppm) ICSS and is not really influenced by the ring current effect of the fluorene moiety. The precise TSNMRS values for the *ortho*-methyl protons, and hence $\Delta\delta_{calcd}$, are given in Table 1 and can be readily compared with $\Delta\delta_{exp}$[20] whereby it can be seen that the agreement between the two is striking.

3.1. *meta*- and *para*-Methyl protons

The δ values of both *meta*- and *para*-methyl protons are only influenced negligibly by the fluorene ring current effect (less than ±0.1 ppm). The corresponding experimental proton chemical shifts

Table 1
Experimental ^{1}H chemical shifts[20] of the methyl protons and proton H-9 at the sp^3-hybridized carbon atom connecting the aryl and fluorene moieties compared with TSNMRS[1] of the fluorene anisotropic effect in 9-arylfluorenes **1**–**5**

No	δ (^{1}H)/ppm					Anisotropic effect of the fluorene moiety			
	ortho	*ortho′*	*meta*/*para*	H-9	$\Delta\delta_{exp}$/ppm	*ortho*	*ortho′*	*meta*/*para*	$\Delta\delta_{calcd}$/ppm
1	1.13	2.63	—	5.30 (4.90)[a]	1.50	1.79	−0.41	—	2.20
2	1.13	2.69	—	5.50	1.56	1.80	−0.34	—	2.14
3	1.10	2.64	2.25	5.47	1.54	1.81	−0.34	−0.02	2.15
4	—	—	2.21	4.97	—	—	—	0.26	—
5	—	—	2.27	4.98	—	—	—	0.04	—

[a] Conformer with the *ortho* methyl above the plane and, in parentheses, in-plane with the fluorene moiety.

Table 2
Geometrical data (dihedral angles/°, distances *r*/Å) of 9-arylfluorenes **1**–**5**

No	<H–C(sp^3)–C(*i*)–C(*o*)[a]	<C(*f*)–C(sp^3)–C(*i*)–C(*o*)[a]	<Plane1, plane2[b]	*r*[H–C(sp^3)···C(*o*)][a]	*r*[H–C(sp^3)···C(*o′*)][a]
1	14.5° (0.0°)[c]	45.3° (59.2°)[c]	83.7° (90.0°)[c]	2.655 Å (2.527 Å)[c]	3.409 Å (3.436 Å)[c]
2	0.0°	59.2°	90.0°	2.527 Å	3.436 Å
3	0.0°	59.5°	90.0°	2.574 Å	3.434 Å
4	0.0° (0.0°)[d]	57.4° (57.3°)[d]	90.0° (90.0°)[d]	2.607 Å (2.613 Å)[d]	3.417 Å (3.416 Å)[d]
5	0.0°	57.4°	90.0°	2.613 Å	3.418 Å

[a] Aryl moiety: *i* (*ipso*), *o*,*o′* (*ortho*); fluorene moiety: *f*, adjacent to C(sp^3).
[b] Angle between the planes of the aryl and fluorene moieties.
[c] Conformer with the *ortho* methyl above the plane and, in parentheses, in-plane with the fluorene moiety.
[d] Conformer with the *meta* methyl above the plane and, in parentheses, in-plane with the fluorene moiety.

in the ^{1}H NMR spectra were found[20] at positions typical for these kinds of methyl protons (2.21–2.27 ppm) and can serve as reference for δ (Me) free of influence from the ring current effect of the fluorene nucleus.

3.2. *ortho*-Methyl protons

The methyl protons above the fluorene moiety, in concert with the TSNMRS, are strongly shielded and in fact are shielded by more than 1.1 ppm compared with the *meta*- and *para*-methyl protons in analogous aryl moieties. The calculated effects, however, are indicated to be larger than what are observed obviously due to competing steric compression, which is active into the opposite sense with regards to chemical shift influence; this competition is inherent and not new.[8,15,16] The second *ortho*-methyl protons, however, due to their in-plane position with the fluorene moiety, are deshielded by 0.48–0.36 ppm (compared with the δ values of *meta*/*para*-methyl protons). This is in complete agreement with the calculated TSNMRS values. In this latter case, obviously steric compression is not in effect and the deshielding of the methyl protons is dictated by the ring current effect only.

3.3. Proton H-9 at the sp^3-hybridized carbon atom

The $\Delta\delta_{calcd}$ between the *o*,*o′*-methyl protons as calculated by our methodology[1] is larger (2.14–2.20 ppm) than experimentally observed (1.50–1.56 ppm) with steric compression having been suggested[8,15,16] as the reason for this disparity. As experimental proof thereof, the chemical shift of H-9 at the sp^3-hybridized carbon can be employed: the anisotropic effect of the aryl moiety on this proton is the same in all arylfluorenes **1**–**5** because the angle between the aryl and fluorene moieties planes remains constant at ca. 90.0° (Table 2). In **1**, due to only one *ortho*-methyl substituent, the planes are slightly twisted by 6.3° relative to each other to partly avoid steric strain; the chemical shift of this proton, however, still changes by nearly the same amount. In **2** and **3**, due to *o*,*o′*-disubstitution, δ values in the range 5.47–5.50 ppm were observed. In the case of *meta* or *para* substitution (**4** and **5**), this proton was found in the region 4.97–4.98 ppm.[20] In the case of **1**, due to some steric relaxation (vide supra), less distinct values at 5.50 ppm and 4.90 ppm were measured. The $\Delta\delta$ between *o*,*o′*-dimethyl substitution (in **2** and **3**) and *meta*-/*para*-methyl substitution (in **4** and **5**) is ca. 0.5 ppm, but because the anisotropic effect of the aryl moiety on this proton must be constant (because of identical dihedral angles between the two molecule moieties), the influence responsible for the $\Delta\delta$ of H-9 can only be steric compression. This is also about the same divergence between the $\Delta\delta$ due to the corresponding anisotropic effect of the fluorene moiety (cf. Table 1) and the experimental $\Delta\delta$ of the *o*,*o′*-methyl protons. The steric compression in **2** and **3** with respect to **4** and **5** is proven by the shorter *r*[H–C(sp^3)···C(*o*)] distance and the adequately larger *r*[H–C(sp^3)···C(*o′*)] distances in the former *o*,*o′*-dimethyl substituted compounds (cf. Table 2).

Not only does the anisotropic effect of the fluorene moiety determine the $\Delta\delta$ of the *o*,*o′*-methyl protons, the differences to the experimental $\Delta\delta$ values have been proven (and not just suggested)[8,15,16] to be generated by steric hindrance in these molecules with similar influences on the H-9 and *o*,*o′*-methyl protons presumed to be in effect.

4. Conclusions

Both the structures of the preferred conformers of various 9-(methyl)arylfluorenes **1**–**5** and the spatial magnetic properties (TSNMRS) of the fluorene moiety have been ab initio MO calculated. In the ground-state conformers, the planes of the aryl and fluorene moieties are perpendicular to each other. The experimental ^{1}H chemical shifts of the methyl protons located at the *ortho*, *meta*, and *para* positions on the aryl moiety[20] in **1**–**5** were examined with respect to the spatial magnetic properties (TSNMRS) of the fluorene moiety and were found to be controlled by the ring current/anisotropic effect of the fluorene moiety and by the steric hindrance present in the molecules. Because of persistently strong reservations to qualifying molecular response properties, such as experimentally proven anisotropic effects of functional or aromatic groups on the ^{1}H chemical shifts of proximate protons by unobservable quantities like NICS,[17] the results of this study can serve as definitive proof of the value of TSNMRS to not only successfully assign the conformation, configuration and diastereoisomerism of structures[2–14] as well as the conformational state if the underlying dynamic process is fast on the NMR timescale,[19] but to generally visualize and quantify the anisotropic effects of functional groups on the ^{1}H NMR chemical shifts, which can be measured experimentally and which can hereby serve as the molecular response property of spatial NICS. The differences between the experimentally observed and calculated chemical shift differences, $\Delta\delta_{calcd}$ and $\Delta\delta_{exp}$, for the *o*,*o*′-methyl protons in the ^{1}H NMR spectra were shown to arise from steric compression.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.005.

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