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Intrinsic Long Range Deuterium Isotope Effects on ^{13}C NMR Chemical Shifts as a Conformational Probe of Benzene Derivatives

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^{13}C NMR spectra of molecules containing one or two benzene rings linked with $CH{=}CH_2$, CH=CH (*trans-* or *cis-*), C≡C and CH=N groups revealed the existence of long range deuterium isotope effects on ^{13}C chemical shifts. It was found that deuterium isotope effects over six bonds ($^6\Delta$) are related to the conformation of investigated molecules. Molecular torsional angles were calculated by *ab initio* HF/6–31G* and AM1 semi-empirical calculations. Very good linear correlations were established between experimentally observed $^6\Delta$ and theoretical torsional angles obtained from *ab initio* and semi-empirical calculations.

Key words: ^{13}C NMR, long range deuterium isotope effects, conformational dependence

INTRODUCTION

Isotope effects in NMR spectra have become a powerful tool for structural studies of various kinds of molecules, including neutral[1] and ionic species.[2] The advent of high-field NMR spectrometers made it possible to deter-

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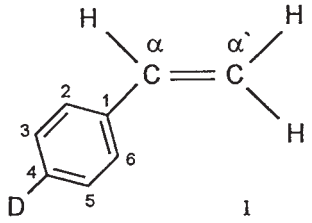
mine minute changes in chemical shifts (even less than 1 ppb)[3] caused by isotopic substitution, which can be transmitted throughout the molecule. Long range isotope effects (LRIE) were observed many bonds away from the site of isotopic substitution and provided information about the molecular geometry and behaviour of molecules in solution.

Isotope effects in NMR spectra are of rotational-vibrational origin, *i.e.* they arise from different averaged nuclear geometry of isotopomers.[4] However, the theory of isotope effects in NMR spectra can be successfully applied only to small and symmetric molecules. In larger systems, high-level quantum chemical calculations of LRIE are not yet completely feasible. For larger molecules, therefore, empirical correlations between LRIE and molecular parameters are the only way to understand isotopic perturbation and elucidate molecular behaviour, particularly properties that cannot be directly measured.

Our recent results for molecules containing one or two phenyl rings linked *via* CH=CH, C≡C, CH=N, N=N, *etc.* groups revealed the influence of the linking group nature, the isotope position and orientation of lone pairs on the magnitude and sign of isotope effects.[3,5] The objective of this article is to present empirical correlations between LRIE and the molecular torsional angle (see Results and Discussion), that may be of importance in conformational analysis. Investigated molecules were benzene derivatives deuteriated at the *para*-position of one benzene ring (Scheme 1).

EXPERIMENTAL

Deuteriated compounds **4**–**8** were prepared using the standard procedures described elsewhere.[5,6] NMR data for compounds **1–3** were taken from the literature.[7] The ^{13}C NMR spectra were recorded with Varian Gemini 300, XL–400, VXR 500S and Inova Unity 600 NMR spectrometers, operating at 75.4, 100.6, 125.7 and 150.8 MHz, respectively. Acetone-d_6 was used as solvent and as internal lock. TMS was used as an internal reference. Spectra were measured in 0.2–0.3 mol/L solutions in 5 mm NMR tubes at 294 K. For precise measurements of long range deuterium isotope effects, the narrow region spectra were recorded with spectral widths 500–2000 Hz, acquisition times 6–10 s and 300–1000 transients per spectrum. The spectra were zero-filled to 64 K, thus giving a digital resolution better than 0.05 Hz per point after Fourier transformation. The assignments were performed on the basis of COSY, NOESY, HETCOR and HMBC spectra. Intrinsic deuterium-induced isotope effects were determined in the conventional way ($\Delta = \delta_H - \delta_D$) from the samples, which contained mixtures of labelled and unlabelled compounds in different ratios. The positive sign denotes an upfield isotope shift. Standard deviations of experimental isotope effects were less than 0.8 ppb. Calculations were performed using MOPAC and Gaussian 94 packages.[8,9] Geometries of all the investigated molecules were optimized at the semi-empirical level using the eigenvector following routine.[10] AM1 Ha-



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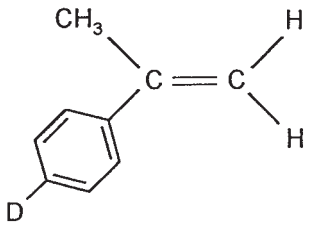

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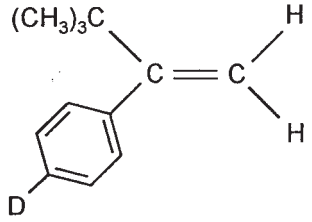

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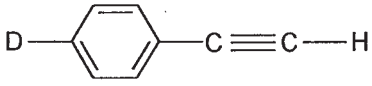

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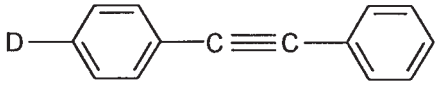

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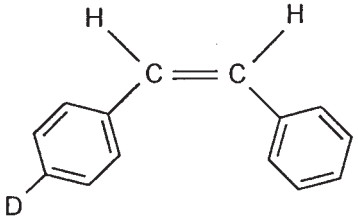

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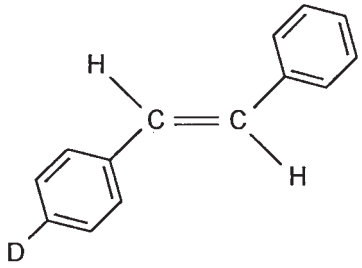

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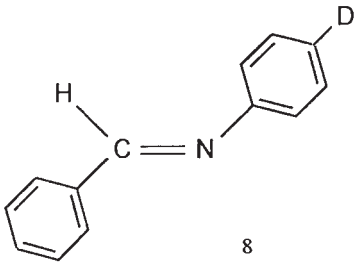

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Scheme 1.

miltonian was used in semi-empirical calculations and HF/6–31G* basis set in *ab initio* calculations. Zero point energy corrections were estimated from the harmonic frequencies calculated at the semi-empirical level and they lower the molecular association energies by *ca.* 1 kcal mol^{-1}.

RESULTS AND DISCUSSION

Table I presents experimental intrinsic deuterium isotope effects on ^{13}C chemical shifts over six-bonds ($^6\Delta$/ppb) and experimental[11] and calculated values of torsion angles ($\phi°$) for a series of *para*-deuteriated benzene derivatives. The torsional angle was defined as an angle between atoms in fragments $C_2{=}C_1{-}C_\alpha{=}C_{\alpha'}$ and $C_2{=}C_1{-}C_\alpha{\equiv}C_{\alpha'}$ or $C_2{=}C_1{-}N{=}C_{\alpha'}$ (Scheme 1). Calculations were performed using semi-empirical AM1 and *ab initio* HF/6–31G* level. The torsional angle values obtained by these two methods differ 1–10°, depending on the nature of the linking group. Such variations in calculated values are not unexpected since they arise from different types of wave functions and the level of the theory applied in semi-empirical and *ab initio* calculations.

All $^6\Delta$ are positive, *i.e.* they are shielding effects, ranging from zero to 15.6 ppb. From Table I, one can see that six-bond effects in the benzene de-

TABLE I

Experimental intrinsic deuterium isotope effects on ^{13}C chemical shifts over six bonds ($^6\Delta$/ppb) and calculated and experimental torsional angles ($\phi°$) in a series of *para*-deuteriated benzene derivatives

p-^{2}H-isotopomer	$^6\Delta$[a]	Torsional angle ($\phi°$)		
		6–31G*[b]	AM1[c]	Exp.[d]
styrene **1**	12.0[d]	18.9	19.9	18
α-CH_3-styrene **2**	9.0[d]	43.0	36.5	43
α-$(CH_3)_3$-styrene **3**	0.0[d]	88.7	75.9	90
phenylacethylene **4**	15.0	0.0[e]	0.0[e]	0
cis-stilbene **5**	8.7	43.6	39.7	43
trans-stilbene **6**	10.2	23.0	22.9	30
tolane **7**	15.6	0.0[e]	0.0[e]	0
trans-N-benzylideneaniline **8**	7.0	44.6	34.8	38

[a] Standard deviations for the observed isotope effects are less than 0.8 ppb. Aceton-d_6 solutions.
[b] *Ab initio* 6–31G* values.
[c] Semi-empirical AM1 values.
[d] Values taken from literature.[7,11,12]
[e] Linear molecule.

rivatives are dependent on torsional angle ϕ. If the angle is larger, the isotope effect is smaller. Therefore, in linear molecules of phenylacethylene, **4** and tolane **5**, the six-bond effects of the largest magnitude were observed, while in highly twisted 1-phenyl-1-*tert*-butylethylene, **3**, the six-bond isotope effect was zero.[7] The following dependence of deuterium isotope effects over six-bonds on the torsional angle ϕ can be proposed:

$$^6\Delta = A \cos^2\phi + B \quad (1)$$

where A and B are empirical parameters.

Thus, a plot of $^6\Delta$ values against $\cos^2\phi$ yielded a straight line for both *ab initio* and semi-empirical values of torsional angles (Figure 1). The linear correlation obtained for *ab initio* calculated values of ϕ is given by equation (2).

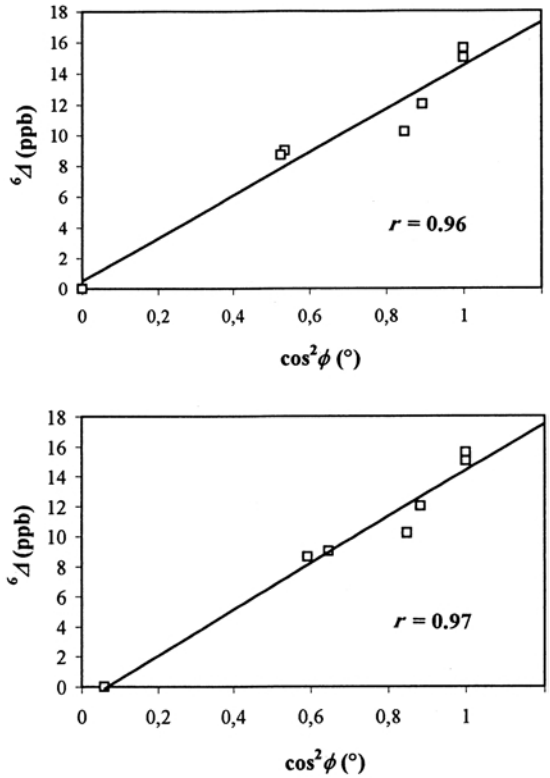

Figure 1. Correlation between experimental intrinsic deuterium isotope effects over six bonds ($^6\Delta$) and calculated torsional angles (ϕ) for a series of *para*-deuteriated benzene derivatives. The straight line obtained from Eq. (2) using *ab initio* (HF/6–31G*) values of ϕ is presented above, while that from Eq. (3), using AM1 semi-empirical values of ϕ is displayed below.

$$^6\Delta = 13.55 \cos^2\phi + 0.55 \ . \quad (2)$$

The correlation coefficient r is 0.96; $A \pm$ SE = 1.19; $B \pm$ SE = 1.59; SABS = 1.17.

In the case of semi-empirical torsional angle values, the linear correlation is presented by equation (3).

$$^6\Delta = 15.58 \cos^2\phi - 1.42 \ . \quad (3)$$

The correlation coefficient r is 0.97; $A \pm$ SE = 1.28; $B \pm$ SE = 1.67; SABS = 1.01.

In order to check the validity and the predictive power of the proposed correlations, we have calculated the torsional $C_2{=}C_1{-}N{=}C_\alpha$ angle in compound **8** using equations (2) and (3). The obtained values of 46.4° and 41.6°, respectively, are in agreement with HF/6–31G* and AM1 calculated values (44.6° and 34.8°) as well as those experimentally observed (30–50°).[11,12] Angular dependence of isotope effects has so far been reported only for short range effects, *i.e.* isotope effects transmitted three bonds away from the isotopic substitution site.[13] We have demonstrated here that even long range deuterium isotope effects, although very small (less than *ca*. 16 ppb), can be very precisely measured and used in conformational studies. If the entire phenyl group is taken as one atom, the resemblance of $^6\Delta$ torsional angle dependence to Karplus angular equation is evident. However, the physical basis of ^3J and $^6\Delta$ is different, since the former is related to σ- and the latter to π-systems.

A remarkable fact is that the magnitude of $^6\Delta$, in the benzene derivatives studied here, is very little affected by other factors contributing to the isotope effect, such as hybridization,[13,14] bond order,[15] hyperconjugation[16] and lone-pair effects.[5,17] If these factors contributed significantly to the observed value of $^6\Delta$, one should not expect a linear correlation for a series of compounds, including sp^2 hybridized atoms as in **1**–**3**, **5** and **6**, sp hybridized atoms as in **4** and **5**, or sp^2 hybridized atoms bonded to heteroatom with lone-pairs as in **8**. The obtained results suggest that the main factor that governs the magnitude of $^6\Delta$ is the twist between the phenyl ring and the linking group, *e.g.* $CH{=}CH_2$, CH=CH, C≡C or CH=N. This twist, *i.e.* the molecular conformation, is a consequence of competition between π-electron conjugation and steric repulsions involving *ortho*-phenyl hydrogens and α-hydrogens or lone-pairs of linking groups. Deuterium LRIE were detected practically only in π-molecules, which means that π-electron transmission is the most important contributing factor. A unique explanation of the behaviour of $^6\Delta$ in *para*-deuteriated benzene derivatives is still difficult, since $^6\Delta$ effects transmitted in the opposite direction, *i.e.* from C-α' to C–4, in the corresponding α'-deuteriated isotopomers do not show a conformational depen-

dence.[1] Our *ab initio* calculations reveal that the C_{para}-H HOMO orbital has a constructive interaction with the π-orbitals of the linking group (CH=CH, CH=N, *etc*.).[18] Most probably, the relative orientation of the π-orbitals plays the major role in terms of the magnitude of the isotope effect. This is in agreement with the recently proposed vibrationally induced π-electron polarization[5] model of transmission of isotope effects in aromatic molecules, which explains the magnitude and sign alternation of the observed long range deuterium isotope effects.

The study on torsional angle dependence of $^6\Delta$ in benzene derivatives reported here points to the practical importance of deuterium LRIE. Further investigations of LRIE, other than $^6\Delta$, could reveal their potential use in conformational analysis. Anyway, there is still much space for research into isotope effects in NMR spectra, both from theoretical and experimental points of view.

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SAŽETAK

Intrinsični deuterijski izotopni učinci dugoga dosega na ^{13}C-NMR kemijske pomake kao konformacijska proba za derivate benzena

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U ^{13}C-NMR spektrima molekula koje su građene od jednog ili dva benzenska prstena na koji su vezane skupine CH=CH$_2$, CH=CH (*trans-* ili *cis-*), C≡C i CH=N, opaženi su deuterijski izotopni učinci dugoga dosega na ^{13}C-NMR kemijske pomake. Utvrđeno je da deuterijski izotopni učinci kroz šest veza ($^6\Delta$) ovise o konformaciji istraživanih molekula. Torzijski kutovi molekula računani su *ab initio* (HF/6–31G*) i semi-empirijskim (AM1) računima. Dobivena je vrlo dobra korelacija eksperimentalno izmjerenih $^6\Delta$ s proračunanim torzijskim kutovima iz *ab initio* i semi-empirijskih računa.