tries. The barrier of 1,3-boron shift is expected to be higher in ether solvent because of dissociation of boron-ether coordination in the transition state.

Conclusion

Ab initio molecular orbital calculations predict that chair transition structures are preferred for the reaction of formaldehyde with allylborane and allylboronic acid. The transition structures found here should be good models for the transition structure of reactions of allyl(dialkyl)borane and allylboronate reactions with carbonyl compounds. Development of a force field to treat stereoselectivity of highly substituted cases efficiently and quantitatively will be reported at a later date.

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Registry No. 1, 51531-21-6; HCHO, 50-00-0; allylboronic acid, 88982-39-2.

Supplementary Material Available: Energies (au) and internal coordinates (lengths in Å, angles and dihedral angles in deg) of the stationary points for the reaction of formaldehyde with allylborane and allylboronic acid and the rearrangement of allylborane (23 pages). Ordering information is given on any current masthead page.

The Angular Dependence of Geminal Deuterium Isotope Effects on ^{13}C NMR Spectra in Carbonyl Compounds

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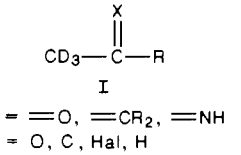
Abstract: The measurement of intrinsic deuterium isotope effects over two bonds in carbonyl compounds reveals a dependence of the dihedral angle between the direction of the π-orbital of the carbonyl group and the direction of the C-D σ-bond. This angular dependence is superimposed on a general dependence between deuterium isotope effects and the chemical shift. The results are discussed in terms of hyperconjugation. Applications of these findings for conformational analysis are shown.

The study of intrinsic deuterium isotope effects on ^{13}C NMR spectra can be of importance in understanding the behavior of the ^{13}C chemical shift,[1,2] The small perturbations caused by the isotope often reflect on a minor scale the action of substituents.[3,4] Because of the vibrational origin,[2] the isotope effects over one or two bonds should be all negative.[5] This implies that in deuterated compounds the carbon atoms are shielded compared with the parent compounds; this is expected owing to the shorter C-D distance caused by a lower zero-point vibration in an asymmetric potential.[2] Exceptions have long been known, however, and a positive isotope effe :t at the carbonyl carbon atom, for example, in deuterated acetone was reported very early.[8] This was recently remeasured and compared with the tritiated compound.[9] In fact, there is a correlation between ^{13}C NMR chemical shifts and the deuterium isotope effect over two bonds ($^2\Delta$) in α-deuterated compounds of type I, spanning a chemical shift range of 150 ppm and deuterium isotope effects between +200 and -200 ppb.[10] A



I

X = =O, =CR_2, =NH
R = O, C, Hal, H

similar relationship was recently published for cations.[11] We had independently found[12] that such a relationship exists not only for sp^2-hybridized carbon atoms but is valid for the complete range of ^{13}C NMR chemical shifts, although exceptions are known.[11] An example is given for some bicyclic compounds in Figure 1. Thus a connection between deuterium isotope effects and chemical shifts of the carbon atoms seems to be more general. We maintained earlier that deuterium isotope effects display on a minor scale the behavior of normal substituents.[13] Therefore, it was tempting to plot substituent-induced shifts versus chemical shifts of the relevant carbon atoms. In Figure 2 the results for the substituent-induced shift of a bromine atom at a β-carbon atom is shown which displays an obvious linear relationship. Preliminary data analysis shows that a relationship as plotted in Figure 2 could possibly be more general.[14]

This explains, for instance, why ^{13}C NMR increment systems only work well for a narrow group of compounds, e.g., substituted benzenes, since the chemical shifts in such a group are all rather similar. A chemical shift dependence of substituent effects could be the underlying reason for the nonadditivity of chemical shifts in para-disubstituted aromatic compounds.[15]

Remarkable in Figure 2 is the sign change of substituent effects. This was found for the geminal isotope effects as well by us and by Arrowsmith and Kresge.[10] Positive and negative isotope effects, however, require, according to these authors, at least two mech-

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(4) Künzer, H.; Berger, S. *J. Am. Chem. Soc.* **1985**, *107*, 2804-2805.
(5) There is considerable confusion about the sign convention of deuterium isotope effects. When we started in this field, we adopted negative signs for upfield deuterium isotope effects.[6] Guided by referees of different journals and in congruence with the leading review articles,[1] we changed the signs in our subsequent papers.[3,4,7] After submission of this paper both referees preferred the other sign. Since in this paper it is shown that deuterium isotope effects behave similarly to substituent effects, we are happy to return to our original sign convention.
(6) Berger, S.; Künzer, H. *Tetrahedron* **1983**, *39*, 1327-1329.
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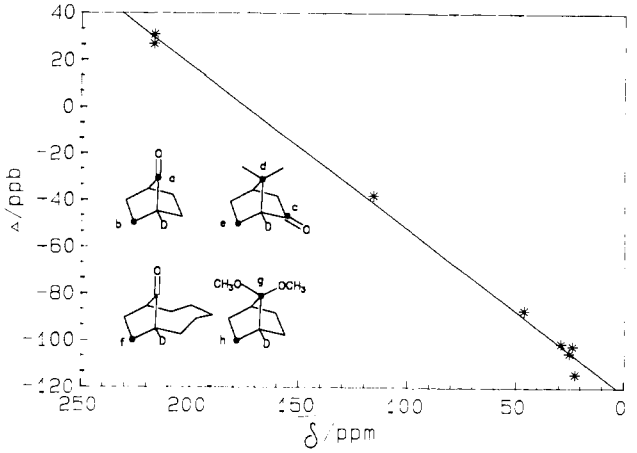

Figure 1. $^2\Delta$ deuterium isotope effects vs. ^{13}C chemical shift of the corresponding carbon atoms in bicyclic compounds [$Y = (0.7 \pm 0.02)X - 121.7 \pm 2$; correlation coefficient, $r = 0.996$].

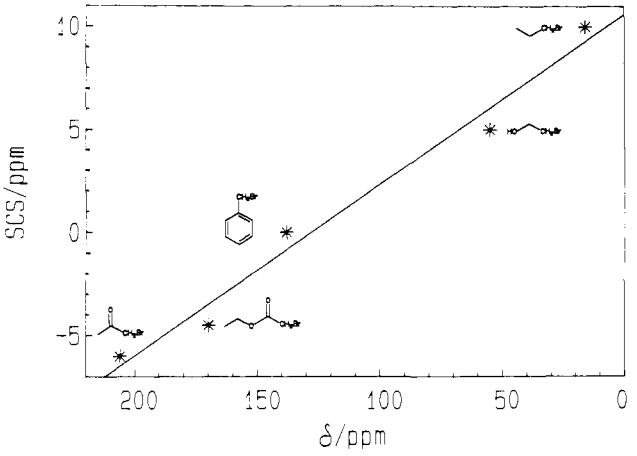

Figure 2. Bromine SCS values vs. ^{13}C chemical shift of the corresponding carbon atoms ($Y = (-0.09 \pm 0.007)X + 11 \pm 0.95$; correlation coefficient, $r = 0.982$).

anisms of isotopic interaction. One mechanism to interpret the relationship between isotope effects and chemical shifts was the different hyperconjugational interaction of the methyl group adjacent to the carbonyl group dependent on the electron demand of the substituent X. Since hyperconjugational interaction is angle dependent, we began to investigate a systematic series of geometrically fixed cyclic and bicyclic ketones, where two more requirements for a stringent analysis were met: the chemical shift or the electron demand at the carbonyl group should be in a narrow range; the substitution pattern at the α-carbon atoms should be comparable, since it is known that substitution alters deuterium isotope effects. For hydrocarbons Günther and co-workers[16] have recently shown a dihedral angle dependence of vicinal deuterium isotope effects, and for carbonyl compounds several other authors have published selected values and argued on conformational dependence.[17-19]

Results and Discussion

In Table I the $^1\Delta$ and $^2\Delta$ deuterium isotope effects, the ^{13}C NMR chemical shifts of the carbonyl group, and the dihedral angles between the deuterium carbon σ-bond and the π-orbitals of the carbon–oxygen double bond of a large series of cyclic and bicyclic ketones are given. The dihedral angles θ were calculated with the MMPMI program.[20] The compounds in Table I are subdivided in four groups: (i) five-membered ring ketones with deuterium at a tertiary carbon atom, (ii) five-membered ring ketones with deuterium at a secondary carbon atom, (iii) six-

Table I. Deuterium Isotope Effects, Chemical Shifts, and Dihedral Angles in Cyclic and Bicyclic Ketones

no.	compound	$^1\Delta^a$	$^2\Delta^a$	δ^b	θ^c
	I. Deuterium at Tertiary Carbon Atoms within Five-Membered Ring Ketones				
1	[1-D]bicyclo[2.2.1]heptan-7-one	−388	27	215.8	90
2	[1-D]7,7-dimethyl-bicyclo[2.2.1]-heptan-2-one	−435	31	216.7	73
3	[1-D]bicyclo[5.2.1]decan-10-one	−407	64	230.0	42
4a	[2-D]-*trans*-2,4-dimethylcyclopentanone	−475	69	221.0	30
4b	[2-D]-*cis*-2,4-dimethylcyclopentanone	−468	98	220.0	8
5	[2-D]-2-methylcyclopentanone	−484	110	221.4	6
	II. Deuterium at Secondary Carbon Atoms within Five-Membered Ring Ketones				
6	[2-D]-cyclopentanone	−328	65	220.0	30
7	[5-D]-2-methylcyclopentanone	−351	57	221.4	30
8[d]	[2-D]-bicyclo[3.3.0]octane-2,7-dione	−331	63	217.7	30
9	[5-D]-2-spirocyclopropylcyclopentanone	−324	63	220.0	30
	III. Deuterium at Tertiary Carbon Atoms in Six-Membered Ring Ketones				
10	[9-D]-*trans*-decalone	−526	97	210.9	23
11	[2-D]-2-methyltetralone-2	−450	78	200.0	23
12	[2-D]-2-methylcyclohexanone	−450	93	211.0	23
13	[2-D]-2-*tert*-Butylcyclohexanone	−509	106	211.3	21
14a	[2-D]-*cis*-2,6-dimethylcyclohexanone	−450	80	212.8	21
14b	[2-D]-*trans*-2,6-dimethylcyclohexanone	−360	47	215.0	50
15	[1-D]-adamantanone	−442	37	216.0	90
	IV. Deuterium at Secondary Carbon Atoms in Six-Membered Ring Ketones				
16	[2-D]cyclohexanone	−330	67	210.0	50
17a	*ax*-[6-D]-2-methylcyclohexanone	−347	80	211.9	21
17b	*eq*-[6-D]-2-methylcyclohexanone	−318	40	211.9	83
18a	*ax*-[6-D]-2-*tert*-butylcyclohexanone	−345	88	211.3	21
18b	*eq*-[6-D]-2-*tert*-butylcyclohexanone	−331	41	211.3	83
19a	*ax*-[2-D]-*cis*-3,5-dimethylcyclohexanone	−370	82	211.0	21
19b	*eq*-[2-D]-*cis*-3,5-dimethylcyclohexanone	−354	43	211.0	83
20	[2-D]-3,3,5,5-tetramethylcyclohexanone	−366	60	212.0	50
21a	*ax*-[2-D]-4-methylcyclohexanone	−361	80	211.4	21
21b	*eq*-[2-D]-4-methylcyclohexanone	−301	40	211.4	83
22	[2-D]-4,4-dimethylcyclohexanone	−319	65	211.2	50
23a	*ax*-[2-D]-4-isopropylcyclohexanone	−352	84	211.0	21
23b	*eq*-[2-D]-4-isopropylcyclohexanone	−316	40	211.0	83
24a	*ax*-[2-D]-*trans*-decalone	−335	81	211.1	21
24b	*eq*-[2-D]-*trans*-decalone	−335	46	211.1	83

[a] Deuterium isotope effect given in ppb; $\Delta = \delta_{labeled} - \delta_{parent}$. [b] Chemical shifts given in ppm vs. TMS. [c] Angles as calculated with the MMPMI program.[20] [d] Equatorial and axial isotope effects identical.

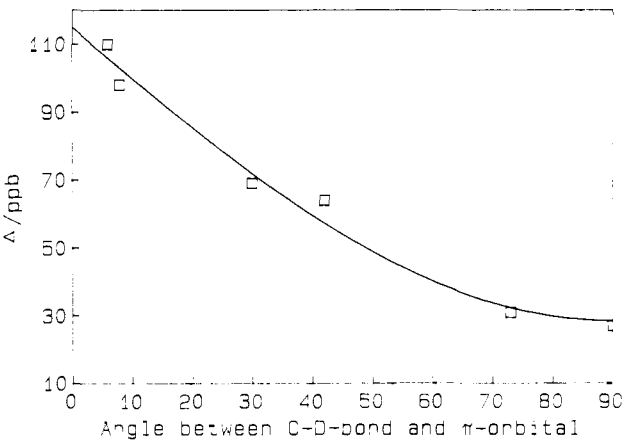

Figure 3. Angular dependence of $^2\Delta$ deuterium isotope effects for compounds **1–5** (eq 1: standard error in offset, ±4; standard error in sine factor, ±6; correlation coefficient, $r = 0.983$).

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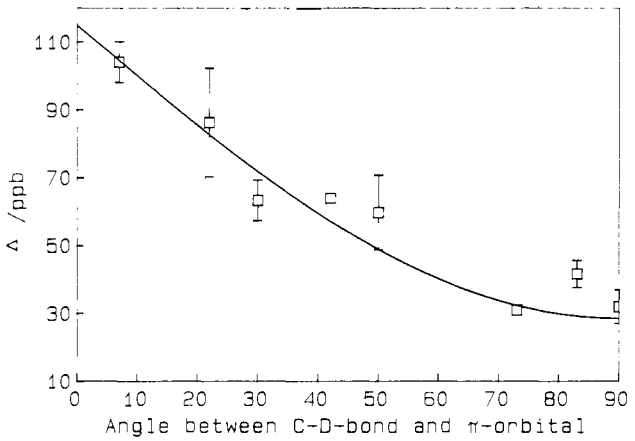

Figure 4. Angular dependence of $^2\Delta$ deuterium isotope effects for compounds **1–24** (eq 1: standard error in offset, ±6; standard error in sine factor, ±8; correlation coefficient, $r = 0.941$].

Table II. $^2\Delta$ Deuterium Isotope Effects and Calculated Dihedral Angle in Open-Chain Ketones

no.	compound	$^2\Delta^a$	θ_{calc} by eq 1	θ_{calc} by MMPMI[b]
25	[1-D]propanone-2	54	47	47
26[c]	[1-D]butanone-2	50	51	47
27[c]	[2-D]pentanone-3	80	23	30
28[c]	[4-D]hexanone-3	73	29	30
29a	[4-D]-2-methylpentanone-3	69	32	30
29b	[2-D]-2-methylpentanone-3	57	43	39
30	[3-D]-3-methylbutanone-2	79	24	35
31	[2-D]-2,4-dimethylpentanone-3	45	57	49

[a] Units and definition as in Table I. [b] Calculations as in Table I. [c] Similar results for several homologous compounds.

membered ring ketones with deuterium at a tertiary carbon atom, (iv) six-membered ring ketones with deuterium at a secondary carbon atom. All compounds are relatively strain free with respect to the deuterated carbon atom.

For the first subclass (i) in Figure 3, a plot of the $^2\Delta$ deuterium isotope effects versus the dihedral angle θ is given. The data were fitted with a sine curve, since for an angular dependence this kind of relationship can be expected, although the data would not exclude a sine square curve, for instance, which was proposed very early for a hyperconjugational relationship in ESR spectroscopy.[21,22] As can be seen, for the rather narrow and well-defined subclass (i), the experimental data do fit nicely the theoretical model. Of course, for a wider range of compounds larger deviations are expected. In Figure 4 a similar plot is given for all compounds of Table I with the error bars indicating the scatter of the data caused by different influences such as ring size, substitution, and others. Nevertheless, the data points still are rather close to the sine curve; thus we conclude that in addition to a general dependence on the chemical shift or electron demand at the carbonyl group, $^2\Delta$ deuterium isotope effects do display an angular dependence, which can be calculated from a sine curve given in the equation:

$$^2\Delta_{[ppb]} = 112.2 - 79.5 \sin \theta \quad (1)$$

A series of open-chain ketones given in Table II can serve as a further test for this model. The conformations of these compounds were again calculated with the MMPMI program. The dihedral angles are compared with the dihedral angles calculated from the deuterium isotope effects using eq 1. The overall agreement is very good and would allow one to use deuterium isotope effects as a tool to determine conformational preference.

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(22) Opposite to footnote 21 we use the angle between C–D σ-bond and the direction of the π-orbitals of the carbonyl group. Hyperconjugation is at maximum, when this angle is 0.

Table III. Deuterium Isotope Effects, Chemical Shifts, and Dihedral Angles in Sterically Hindered Ketones

no.	compound	$^1\Delta^a$	$^2\Delta^a$	δ^b	θ^c
32	[6-D]-2,2,6-trimethylcyclohexanone	−426	55	216.0	23
33	*endo*-[1-D]-2,5-methano-1*H*-inden-7(4*H*)-one, hexahydro (protoadamantanone)	−359	62	219.6	8
34	[3-D]-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one	−296	40	219.1	28
35a	*exo*-[3-D]bicyclo[2.2.1]heptane-2-one	−337	53	216.8	30
35b	*endo*-[3-D]bicyclo[2.2.1]heptane-2-one	−346	42	216.8	30
36a	*exo*-[2-D]bicyclo[3.2.0]heptan-3-one	−357	83	220.0	10
36b	*endo*-[2-D]bicyclo[3.2.0]heptan-3-one	−357	32	220.0	50
37	[3-D]bicyclo[2.2.2]octanone	−346	53	215.5	30

[a] Deuterium isotope effect given in ppb; $\Delta = \delta_{labeled} - \delta_{parent}$. [b] Chemical shifts given in ppm vs. TMS. [c] Angles as calculated with the MMPMI program.[20]

Table IV. $^2\Delta$ Deuterium Isotope Effects and Calculated Dihedral Angle in Sterically Hindered Open-Chain Ketones

no.	compound	$^2\Delta^a$	θ_{calc} by eq 2	θ_{calc} by MMPMI[b]
38	[1-D]-3,3-dimethylbutanone-2	41	40	47
39	[4-D]-2,2-dimethylpentanone-3	48	32	30
40	[4-D]-2,2,4-trimethylpentanone-3	18	0	0

[a] Units and definition as in Table I. [b] Calculations as in Table I.

Steric Influences

There are, however, a number of cyclic ketones whose $^2\Delta$ values do not fit eq 2. These compounds are given in Table III. At closer inspection all these compounds have considerable steric strain at the carbon atom which bears the deuterium because of nonbonded hydrogen–hydrogen interaction. This results in more positive $^2\Delta$ isotope effects. If one fits these data again with a sinusoidal model, we obtain a similar curve as given above and the values fit to the equation:

$$^2\Delta_{[ppb]} = 79 - 59 \sin \theta \quad (2)$$

The corresponding open-chain compounds with a tertiary butyl group adjacent to the carbonyl group are given in Table IV. Again their conformational values agree with the dihedral angles calculated from eq 2.

Conclusion

We have demonstrated in this paper that substituent and isotope effects in ^{13}C NMR depend on the ^{13}C chemical shift of the carbon atom in question. Superimposed on this relationship is an angular dependence for deuterium isotope effects in carbonyl compounds, which can be used for conformational analysis. The use of deuterium isotope effects for conformational analysis is, however, only justified after calibration of a closely related series with similar steric and electronic effects as well known from Karplus relationships for vicinal spin coupling constants.[23]

Experimental Section

The ketones used were mostly commercially available or otherwise prepared by standard literature procedures. For deuteration the ketones were monobrominated in the α-position with NBS[24] or directly with bromine.[25] Monodeuteration was achieved by refluxing the bromo ketones with a copper–zinc catalyst in dry THF and D_2O.[26] Excess D_2O was avoided in order to prevent multiple deuteration. The compounds prepared in this manner were monolabeled with deuterium to about 80% as determined by mass spectroscopy. Purification of the compounds was achieved by preparative GLC chromatography (A 90-P3 Aerograph, column 5% SE 30 on Chromosorb G, AW-DMCS, 60–80 mesh, 1.8 m, $^1/_4$ in., helium flow rate 120–130 mL/min).

The ketones **1**, **2**, and **15** which are not enolizable were deuterated via the corresponding α-halides with tri-*n*-butyltin deuteride.[27]

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A simpler method of deuteration was the catalytic exchange of deuterium between acetone-d_6 and the cyclic ketones directly in the NMR tube. As catalyst traces of HCl gas were used, this method yields mixtures of mono-, di-, tri- and tetradeuterated compounds which can, however, be distinguished in most cases. A third method of deuteration was the exchange catalyzed by neutral Al_2O_3. For this purpose the ketone was dissolved in acetone-d_6 and fed through a small capillary filled with Al_2O_3 with a contact time of about 1 min. The spectroscopic results for the monodeuterated compounds were not influenced by the method of the deuteration.

NMR Measurements. The room-temperature 100.6-MHz ^{13}C NMR spectra were taken at 303 K on a Bruker AM-400 spectrometer equipped with an 256K Aspect 3000 computer using acetone-d_6 solutions or in some cases $CDCl_3$, with small detectable difference of the deuterium isotope effects. The measurements were always performed on mixtures of labeled and unlabeled compounds as given above. The spectral width was set at narrow as possible and separate for the carbonyl and aliphatic regions, typically between 1000 and 4000 Hz. Zero filling to 64K gave a digital resolution better than 0.1 Hz/pt after the Fourier transform. Gaussian multiplication was used to increase the resolution.

The force-field calculations were performed on an IBM-AT personal computer with mathematical coprocessor and EGA graphic equipment.

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (Be 631/6-3).

Proton On-Resonance Rotating Frame Spin–Lattice Relaxation Measurements of B and Z Double-Helical Oligodeoxyribonucleotides in Solution

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Abstract: A method is proposed to account for proton on-resonance rotating frame spin–lattice relaxation, $R_{1\rho}$, of biological macromolecules in solution. The $R_{1\rho}$ measurements detect motions in a time range of the inverse of the frequency of the spin-locking field, ω_1 (tens of kilohertz). The $R_{1\rho}$ time scale (microsecond) is significantly different from those accessible by the usual solution ^1H NMR techniques (nanosecond for R_1 and NOE and millisecond for R_2 and line-shape analysis). The proposed $R_{1\rho}$ method would be conveniently utilized to monitor DNA stiffness in the time range of $1/\omega_1$. As an application of the $R_{1\rho}$ measurements, internal motions of B- and Z-type d(CG)$_3$ are studied in 2 M $NaClO_4$ solution. Results of the $R_{1\rho}$ measurements demonstrate that both the B- and Z-d(CG)$_3$ possess the internal motions in the time range of $1/\omega_1$, but the magnitude of $R_{1\rho(ex)}$ for the B- and Z-d(CG)$_3$ is significantly different. The Z-d(CG)$_3$ has $R_{1\rho(ex)}$ a factor of 2- and 3-fold larger than the B-d(CG)$_3$ under identical conditions at this time scale.

It has been recognized that the structure of DNA molecules must be considered dynamic rather than static. Internal mobilities may play pivotal roles in the recognition of the DNA sequences and in the expression of their biological functions.[1] Along this line, various NMR relaxation studies on large fragments of DNA molecules have been conducted and have shown that double-stranded DNAs are not rigid, but experience fluctuations in the base and phosphate backbone.[2-6] Recently, the internal mobilities of the B and Z DNA have been studied by a number of biophysical chemists to demonstrate the sequence dependence of conformational change and dynamics.

With respect to the internal motions of the DNA molecules, contradictory results between the B and Z DNA have been reported. For example, fluorescent polarization measurements[7] indicate that the Z-form DNA is considerably more mobile than the B form, but light-scattering measurements[8] support the opposite. The proton-exchange rates of the Z DNA are much slower than those of the B DNA.[9,10] Recent NMR relaxation studies[11] show that the internal motions are similar or comparable in both conformations. These discrepancies might arise from the comparison of the internal motions occurring at different time scales.

Various ^1H NMR techniques have been used to monitor the dynamics of DNA in solution. The measurements of spin–lattice relaxation (R_1), sometimes referred to as laboratory frame spin–lattice relaxation, and NOE are the most widely used. These are sensitive to the motions characterized by the Larmor frequency of the observed nuclei which is of the order of 10^{-9}–10^{-10} s (nanosecond) for ^1H on modern high-resolution NMR spectrometers. The spin–spin relaxation measurements (R_2) and line-shape analyses, on the other hand, provide information on the exchange lifetimes in the chemical shift difference time scale which is of the order of 10^{-3} s (millisecond).

By contrast, on-resonance spin–lattice relaxation rates in the rotating frame, $R_{1\rho}$, are the rate constants characterizing the decay of the magnetization of the signals spin-locked by the radio frequency field (rf), $\omega_1 = \gamma B_1$, rotating in the plane normal to the static magnetic field, B_0. Consequently, the observed relaxation rates, $R_{1\rho(obsd)}$, depend on the spectral density governed by ω_1 used in the experiments. The internal motions occurring at or near the frequency of ω_1 fields (tens of kilohertz) can contribute to the

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