Anomeric and Conformational Deuterium Isotope Effects in Saturated Sulphur and Nitrogen Heterocycles

Frank A. L. Anet* and Max Kopelevich

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90024, U.S.A.

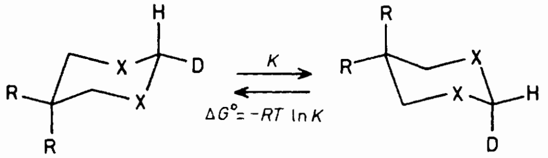
Gas phase Fourier transform i.r. and solution 500 MHz ^{1}H n.m.r. measurements show that deuterium prefers the equatorial over the axial site in *N,N'*,5,5-tetramethylhexahydro[2-^{2}H$_1$]pyrimidine by 420 J mol^{-1}, but exhibits no preference in the case of 5,5-dimethyl[2-^{2}H$_1$]-1,3-dithiane.

We have recently investigated the magnitude and the origin of deuterium isotope effects on the conformational equilibria in [^{2}H$_1$]cyclohexane (**1**)[1] and 5,5-dimethyl-[2-^{2}H$_1$]-1,3-dioxane (**2**).[2] The large difference between the isotope effects in these two compounds (Table 1) and the current interest in anomeric effects involving second-row elements[3—6] prompt us to report data on the sulphur analogue of (**2**), namely, 5,5-dimethyl-[2-^{2}H$_1$]-1,3-dithiane (**3**). Data on the nitrogen heterocycle, *N,N'*,5,5-tetramethylhexahydro[2-^{2}H$_1$]pyrimidine (**4**) are also presented.

Table 1. N.m.r. data and conformational free energy differences (isotope effects).

Compound	$\delta_e - \delta_a$/p.p.m.[a]	$\Delta\delta$/p.p.m.[b]	ΔG°/J mol^{-1}
(**1**)[c,d]	0.478	0.0025	25 ± 5
(**2**)[e,f]	0.470	0.0194	205 ± 15
(**3**)[g,f]	0.225	0.0000	0 ± 5
(**4**)[g,f]	0.330	0.0258	420 ± 30

[a] Measured under conditions of slow ring inversion at low temperatures and extrapolated to room temperature. [b] Measured under conditions of rapid ring inversion at, or slightly above, room temperature. [c] Ref. 1. [d] For ring protons. [e] Ref. 2. [f] For the C-5 *gem*-dimethyl groups. [g] *Ca.* 1% solution in CD_2Cl_2.



	R	X
(**1**)	H	CH_2
(**2**)	Me	O
(**3**)	Me	S
(**4**)	Me	NMe

The conformational properties of the undeuteriated heterocycles corresponding to (**3**) and (**4**) have been extensively studied,[7,8] and the deuteriated analogues (**3**) and (**4**) are readily prepared by modifications of known procedures.[9,10] These deuteriated compounds, like (**2**), are well suited for applying Saunders' isotopic perturbation method,[2,11] as the probe methyl groups at C-5 are well removed from the site of deuteriation at C-2. Both *N*-methyl groups in the non-deuteriated analogue of (**4**) are known to be equatorial.[8]

The 500 MHz ^1H n.m.r. spectrum of the $[2\text{-}^2H_2]$-1,3-dithiane at 23 °C shows an unsplit resonance (0.35 Hz full width at half height) for the geminal methyls. The axial–equatorial chemical shift difference for the methyl protons was measured under conditions of slow ring inversion (−60 to −80 °C) and extrapolated to 23 °C (Table 1). Since this shift difference is relatively large (110 Hz) and the C-5 methyl band is unsplit at room temperature, the isotope effect for the conformational equilibrium in (**3**) must be essentially zero.

The 500 MHz ^1H n.m.r. spectrum of the hexahydropyrimidine (**4**) at 50 °C shows two peaks for the geminal methyl groups (Table 1). The presence of about 15% of the non-deuteriated compound in the sample[10] gives rise to a third methyl peak exactly half-way between these peaks, thus supporting the assumption that the intrinsic deuterium isotope effects[12] on the C-5 methyls are negligible. An extrapolated value for the methyl axial–equatorial chemical shift difference (Table 1), obtained from data in the range of −40 to −70 °C, gives a ΔG° of 420 ± 30 J mol^{-1} for the conformational equilibrium in (**4**). Quantitative integration of the C-1 proton peaks at low temperature was unsatisfactory because of the overlap of the peaks of the deuterio and non-deuterio compounds. However, the equatorial deuterium conformer of (**4**) was clearly predominant.

The C–D stretching frequencies in the i.r. spectra of gaseous (**3**) and (**4**) support the results obtained by n.m.r. spectroscopy. In contrast to the situation in (**2**),[2] only a single C–D stretching band is observed in (**3**) (Figure 1), indicating that the stretching force constants for the axial and equatorial bonds at C-2 are virtually the same. This result is in agreement with an earlier i.r. study on selectively deuteriated 1,4-dithiane and 1,4-oxathiane.[13,14] Moreover, the differences in the C–D bending vibrations of the two conformers of (**3**) must be very small, unless the isotope effects from the two bending modes cancel each other, which appears unlikely. Figure 1 shows that the C–D axial and equatorial stretching bands in the hexahydropyrimidine (**4**) differ in frequency by 247 cm^{-1}, thus giving a zero point energy contribution of 590 J mol^{-1} to ΔG°, some 80% larger than the corresponding value for the 1,3-dioxane (**2**).† Bending contributions of about −170 J mol^{-1} are needed to match the i.r. data to the observed isotope effect of 420 J mol^{-1} in (**4**). It is expected that the bending frequencies for the sterically hindered axial C–H will be higher than those for the equatorial C–H, as is the case in the oxygen analogue.[2] The conformational dependence of the stretching frequency exhibited by a C–H moiety α to a nitrogen atom is related to the well known Bohlmann bands in alkaloids,[15] and is also found in simple amines.[16]

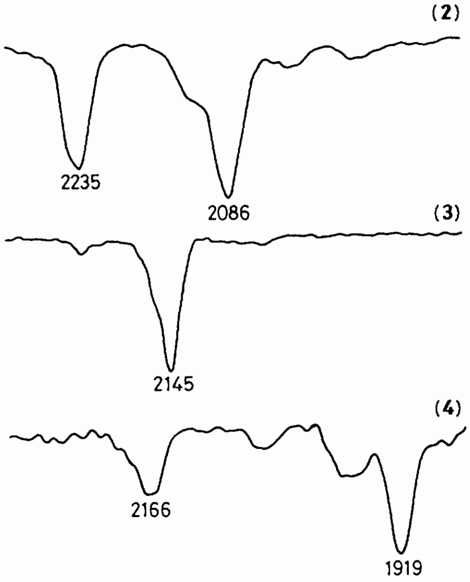


Figure 1. Gas-phase i.r. spectra (Nicolet SX60 GC/IR) in the C–D stretching region of the 1,3-dioxane (**2**), the 1,3-dithiane (**3**) and the hexahydropyrimidine (**4**). Absorption maxima are given in cm^{-1}.

The absence of an isotope effect on the conformational equilibrium in the 1,3-dithiane (**3**), together with the unperturbed axial C–D stretching frequency in this molecule, indicate that the lone electron pairs on sulphur (n_S) are not involved in n_S–$\sigma^*_{C\text{-}H(D)}$ negative hyperconjugation (the stereoelectronic interaction that is at least in part responsible for the anomeric effect[17]). Therefore, the predominant axial orientation of the C-2 substituents such as SePh or $POPh_2$ in 1,3-dithianes,[5,6] and of electronegative groups in thianes[18] must originate from an interaction other than π-donation by sulphur, as has already been surmised by Juaristic *et al.*[5] On the other hand, our n.m.r. and i.r. spectroscopic data confirm

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† The equatorial C–D stretching frequency for (**2**) given previously[2] should have been 2231 instead of 2131 cm^{-1}; however, the zero point energy difference quoted in this reference is correct. More accurate i.r. data for (**2**) are shown in Figure 1 of the present paper.

the importance of the n_N–$\sigma^*_{C\text{-}H(D)}$ and n_O–$\sigma^*_{C\text{-}H(D)}$ hyperconjugative interactions in (**2**) and (**4**), thus suggesting that the anomeric effects observed for the C-2 substituted 1,3-dioxanes and hexahydropyrimidines, as well as other oxygen and nitrogen containing compounds, have important contributions from 'double bond–no bond' resonance.

The present work demonstrates that deuterium is a valuable substituent for isolating the effect of hyperconjugation on the anomeric effect, because dipole–dipole interactions, which can be more or less important with other substituents,[17,18] are absent with deuterium, at least within the Born–Oppenheimer approximation.

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