

It would have been difficult to predict beforehand the magnitude of this splitting for the thymine protons in these concentrated DNA solutions (at 95°) on the basis of the purine-pyrimidine nucleoside shifts reported in this work. Shifts of 5–10 c.p.s. were observed in mixtures of 0.1 *m* thymidine and 0.2 *m* purine.

Jardetzky<sup>6</sup> has compared the proton resonance shifts of 0.2 *M* mononucleotide solutions with the corresponding polynucleotide solutions (0.2 *M* in mononucleotides). The differences, termed "polymerization shifts," were found to be 20–40 c.p.s. upfield for base protons and H-1' of the AMP-poly-A pair. From our earlier work<sup>5</sup> upfield shifts for purine over the concentration range 0.0–0.2 *m* were 12–20 c.p.s., while over the range 0.0–1.0 *m*, 30–40 c.p.s. values were obtained. The magnitude of these latter shifts, originating from association of monomers, is therefore comparable to the "polymerization shifts." It is to be noted that the bases in the polymer are held rigidly at a certain intramolecular distance from each other.

The major question, however, is whether or not the properties of adenine and guanine can be approximated by purine as a substitute. Owing to solubility restrictions, it has not been possible until quite re-

cently to obtain data on adenine-adenine or adenine-thymine interactions at the nucleoside level in water. Now, however, we are able to take advantage of the high solubility of 2'-O-methyladenosine to study these interactions. The data indicate that increase in concentration of 2'-O-methyladenosine does result in upfield shifts for adenine protons in homogeneous solution and for thymine and adenine protons in nucleoside mixtures. The values were about the same as the purine-induced shifts at the same concentration.<sup>17</sup>

The results of this communication lead quite logically to studies of base-base interactions in mono-, di-, and oligonucleotides. These investigations are currently in progress.

*Acknowledgments.* We are grateful to Miss Susan Lowder for her assistance in obtaining many n.m.r. spectra. We are also indebted to Dr. Donald Hollis and Dr. Winslow Caughey of the Department of Physiological Chemistry, School of Medicine, The Johns Hopkins University, for many helpful discussions, advice, and the use of their A-60 spectrometer.

(17) A. D. Broom, M. P. Schweizer, and P. O. P. Ts'o, unpublished results.

## Communications to the Editor

### The Effects of Steric Compression on Chemical Shifts in Half-Cage and Related Molecules<sup>1,2</sup>

Sir:

The effects of steric compression, both intermolecular<sup>3</sup> and intramolecular,<sup>4</sup> on chemical shifts have been reported numerous times. In general, a low-field shift (*ca.* 0.1–0.6 p.p.m. for protons attached to carbon) is observed, irrespective of the nature of the atom which is in juxtaposition to the proton being examined.

We now report a new kind of steric compression effect, *viz.*, a shielding of one of the protons in a CH<sub>2</sub> group when the other proton is strongly compressed

(1) (a) Research was supported in part by National Science Foundation Grants No. G-7423 and GP 3780. (b) Research was sponsored in part by the U. S. Army Research Office (Durham). (c) Research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund.

(2) Reported in part at the Symposium on Cagelike Molecules at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1, 1964.

(3) (a) The effect of pressure on the chemical shifts of compounds in the gaseous state has been studied: S. Gordon and B. P. Dailey, *J. Chem. Phys.*, **34**, 1084 (1961); W. T. Raynes, A. D. Buckingham, and H. J. Bernstein, *ibid.*, **36**, 3481 (1962); (b) solvent effects are also relevant to this problem: A. A. Bothner-By, *J. Mol. Spectry*, **5**, 52 (1960); A. D. Buckingham, T. Schaefer, and W. G. Schneider, *J. Chem. Phys.*, **32**, 1227 (1960); T. Schaefer, W. F. Reynolds, and T. Yonemoto, *Can. J. Chem.*, **41**, 2969 (1963).

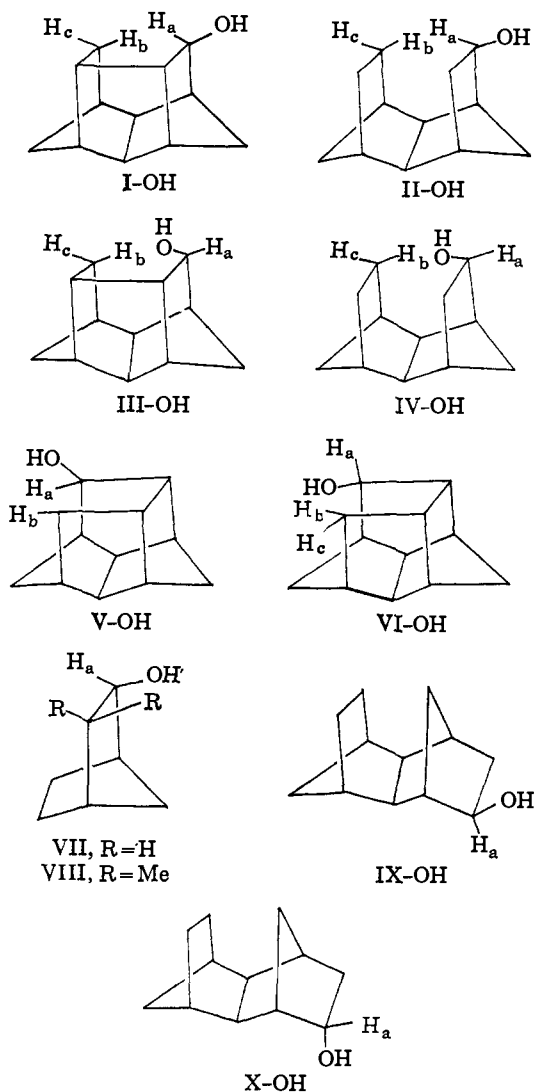
(4) C. Reid, *J. Mol. Spectry*, **1**, 18 (1957); W. Nagata, T. Terisawa, and K. Tori, *J. Am. Chem. Soc.*, **86**, 3746 (1964); D. R. Arnold, D. J. Trecker, and E. B. Whipple, *ibid.*, **87**, 2596 (1965). Many other papers, too numerous to enumerate here, refer to small low-field shifts, which have often been ascribed to van der Waals interactions.

by an oxygen function. We also report some unusually large deshielding effects (1–4 p.p.m.).

The compounds we have examined (I–IV) have the half-cage or *endo,endo*-fused skeletons related to the birdcage hydrocarbon.<sup>5</sup> With their rigid geometries and enormous H–H or H–O steric oppositions, they are ideally suited for the study of effects of steric compression on chemical shifts. These compounds are already known to display C–H stretching bands at abnormally high frequencies ascribed to a strong compression of at least one CH group.<sup>5b,d</sup>

As is clear from the data summarized in Table I, the inside protons are strongly deshielded. The  $\alpha$  proton, H<sub>a</sub>, in the O-outside half-cage alcohol I-OH ( $\tau$  5.52) is at much lower field than the corresponding proton in the *endo,exo*-fused isomer IX-OH ( $\tau$  6.52) or in the simpler model compound, *exo*-norborneol (VII,  $\tau$  6.48). This observed  $\Delta\delta$  of *ca.* 1 p.p.m. is a minimum figure for the size of the steric effect on chemical shift because of the effect of magnetic anisotropy of nearby

(5) (a) S. Winstein, *Experientia Suppl.*, **2**, 137 (1955); (b) L. de Vries and S. Winstein, *J. Am. Chem. Soc.*, **82**, 5363 (1960); (c) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind.* (London), 405, 590 (1960); (d) D. Kivelson, S. Winstein, P. Bruck, and R. L. Hansen, *J. Am. Chem. Soc.*, **83**, 2938 (1961); (e) R. Howe and S. Winstein, *ibid.*, **87**, 915 (1965); (f) compounds I-OH, m.p. 131–132°, and II-OH, m.p. 108–109°, have been previously reported.<sup>5a-c</sup> The III-OH, m.p. 197–198°, was obtained by lithium aluminum hydride reduction of the half-cage ketone, m.p. 165–167°, and IV-OH, m.p. 90–91°, was similarly prepared from the corresponding ketone, m.p. 70–71°, 90–91° (two melting points). Satisfactory carbon and hydrogen analyses were obtained for the new compounds reported.



C-C bonds present in I-OH, but not VII. For example, the corresponding H<sub>a</sub> in *exo*-camphenilol (VIII)

Table I. Summary of Chemical Shifts

Compound	Solvent	Chem. shifts ( $\tau$ values)		
		H <sub>a</sub>	H <sub>b</sub>	H <sub>c</sub>
I-OH	CCl <sub>4</sub>	5.52	>7.6	<8.9
II-OH	CCl <sub>4</sub>	5.46	>7.5	<9.0
III-OH	CCl <sub>4</sub>	6.08	6.45	9.12
III-OH	DMSO <sup>a</sup>		(6.1-6.2)	9.23
III-O <sup>-</sup> Na <sup>+</sup> <sup>b</sup>	DMSO	5.75	4.72	9.40
III-OAc	CCl <sub>4</sub>	5.37	7.00	9.07
IV-OH	CCl <sub>4</sub>	5.78	7.05	<8.8
IV-OMe	CCl <sub>4</sub>	6.23	7.18	<8.9
IV-OAc	CCl <sub>4</sub>	5.17	7.47	<8.8
IV-OBs <sup>c</sup>	CCl <sub>4</sub>	5.28	>7.6	<8.8
V-OH	CCl <sub>4</sub>	6.15	>7.3	<8.6
VI-OH	CCl <sub>4</sub>	5.81	>7.5	<8.8
IX-OH	CCl <sub>4</sub>	6.52		
X-OH	CCl <sub>4</sub>	6.04		

<sup>a</sup> Dimethyl sulfoxide. <sup>b</sup> The sodium salt was obtained by adding an excess of CH<sub>3</sub>SOCH<sub>2</sub>-Na<sup>+</sup> in DMSO to the alcohol dissolved in DMSO. <sup>c</sup> *p*-Bromobenzenesulfonyl.

is at  $\tau$  6.87. Thus, the steric deshielding effect on H<sub>a</sub> due to the proximity of H<sub>b</sub> in I-OH is seen to be in excess of 1 p.p.m. A deshielding of essentially the

same magnitude is observed on the inside H<sub>a</sub> due to proximity to H<sub>b</sub> in the O-outside *endo,endo*-fused alcohol II-OH (Table I). The same kind of deshielding ( $\Delta\delta$  ca. 1 p.p.m.) of the four inside protons in the parent hydrocarbon II-H related to II-OH is apparent on comparing the n.m.r. spectrum of II-H with that of the isomeric IX-H or the simpler norbornane. Similarly, the *endo* proton vicinal to the carbonyl group in the *endo,endo* ketone II=O is deshielded ( $\Delta\delta$  ca. 1 p.p.m.) relative to the corresponding *endo* proton in IX=O. As regards the scope of this type of deshielding, it is pertinent that any such effect on the inside H<sub>a</sub> proton in the O-outside alcohol in the less congested isomeric half-cage system<sup>5c</sup> is much smaller (Table I).

Of even greater interest are the low-field shifts of the inside H<sub>b</sub> protons opposed to a functional group in the O-inside alcohol III-OH and IV-OH and their derivatives. If one takes the "normal" chemical shift of H<sub>b</sub> as that of the *endo* protons in norbornane<sup>6</sup> ( $\tau$  8.8), the deshielding effects on H<sub>b</sub> are given as ca. 2.4 p.p.m. in half-cage III-OH and 1.7 p.p.m. in *endo,endo* IV-OH. In general, these effects are seen to be larger in the more rigid half-cage derivatives than in the *endo,endo* analogs, compromises in the geometry to lessen the steric interaction being more difficult in the former than in the latter. Consistently, no effect on H<sub>b</sub> is observed with the O-inside alcohol in the less congested isomeric half-cage system<sup>5c</sup> VI (Table I).

The size of the effect on H<sub>b</sub> varies with the nature of the functional group in juxtaposition with it, the deshielding effects being in the sequence O<sup>-</sup>Na<sup>+</sup> > OH > OMe > OAc > OBs. With the O<sup>-</sup>Na<sup>+</sup> group in the half-cage III-O<sup>-</sup>Na<sup>+</sup>, H<sub>b</sub> is *deshielded* by as much as 4 p.p.m. This variation in the shift of H<sub>b</sub> is in the exact order of the electron density at the oxygen atom.<sup>7,8</sup> The same type of relationship has been observed for solvent effects,<sup>3b</sup> and especially for hydrogen bonding.

Completely unprecedented is the observation that the outside H<sub>c</sub> protons on the methylene group in juxtaposition to the inside OR groups in the more rigid half-cage systems also show a chemical shift, this time to *higher* field.<sup>9</sup> Taking the *exo* protons in norbornane<sup>6</sup> as reference ( $\tau$  8.6), the shielding effect on H<sub>c</sub> is ca. 0.5 p.p.m. in III-OH and 0.7 p.p.m. in III-ONa. Thus, the shielding effects on H<sub>c</sub> parallel the deshielding ones on H<sub>b</sub>. A possible explanation is that the electron cloud of the oxygen function tends to shift the bonding electrons in the grouping H<sub>c</sub>CH<sub>2</sub> away from H<sub>b</sub> and toward H<sub>c</sub>, thus accounting in part for the lower shielding of H<sub>b</sub> and the higher shielding of H<sub>c</sub>. While this effect on H<sub>c</sub> is not yet well understood, it is interesting to note that, while the H<sub>c</sub> chemical shift is affected by the inside H<sub>b</sub>-OR juxtaposition, no effect is visible on the outside H<sub>a</sub> proton on the ROCH<sub>a</sub> group.

(6) A. Nickon and J. H. Hammons, *J. Am. Chem. Soc.*, **86**, 3322 (1964).

(7) In steroids, an axial hydroxyl group in a 1,3 relationship to an axial methyl group deshields the methyl protons by ca. 0.2 p.p.m. [J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958)]. Here also, acetylation of the hydroxyl group decreases the deshielding of the methyl protons [Y. Kawazoe, *et al.*, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962)].

(8) Calculations have been reported which show that a CH proton is deshielded by the electric field of a nearby charge: A. D. Buckingham, *Can. J. Chem.*, **38**, 300 (1960).

(9) The value of  $|J_{bc}|$  in III and IV derivatives was almost constant ( $\sim 12$  c.p.s.) and was employed to identify H<sub>b</sub> and H<sub>c</sub>. The assignment of the H<sub>b</sub> and H<sub>c</sub> bands was confirmed by decoupling experiments.

Thus, the chemical shifts of  $H_a$  in the III, IV, and VI derivatives appear quite normal.

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Received August 2, 1965

### Effects of Steric Compression on Coupling Constants<sup>1,2</sup>

Sir:

Compounds with a half-cage structure related to the birdcage hydrocarbon are very useful for studying the effects of steric compression on chemical shifts.<sup>3</sup> We now report that steric compression in this series of compounds leads also to unusual coupling constants and relaxation effects and that the results have an important bearing on the existence of a "through-space" mechanism<sup>4</sup> for spin coupling.

The compounds with which we are concerned are half-cage O-inside derivatives I<sup>5</sup> and II<sup>3</sup> and the O-outside analogs III.<sup>5</sup> In the O-inside alcohols I-OH and II-OH coupling between the inside  $H_b$  proton and the hydroxyl proton  $H_o$  (and perhaps even between  $H_b$  and the outside  $H_a$   $\alpha$  proton) is conceivable, as is also coupling<sup>6</sup> between the two inside  $H_b$  and  $H_a$  protons in III.

Chemical shifts of  $H_a$ ,  $H_b$ , and  $H_o$  in the various derivatives are summarized in Table I. For observation of  $H_b$ - $H_o$  coupling, spectra were determined in acetone solution, conditions which are known to give very slow exchange of hydroxyl protons.<sup>7</sup> The temperature-dependent bands clearly belong to  $H_o$ . The other bands can be assigned on the basis of the expected chemical shifts for inside and outside protons and on the expected relative complexity of the bands of  $H_a$  and  $H_b$  as a result of coupling of  $H_a$  to  $H_d$ , etc. Comparison of the hexachloro compounds with their unchlorinated analogs<sup>3</sup> suggests that the deshielding of the inside protons tends to be even larger in the former derivatives than in the latter. In particular the deshielding of  $H_b$  on going from O-outside to O-inside compounds is

(1) Research was supported in part by National Science Foundation Grants No. G-7423 and GP 3780. (b) Research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of this fund.

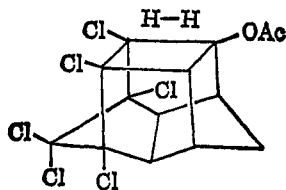
(2) Reported in part at the Symposium on Cagelike Molecules at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1, 1964.

(3) S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Am. Chem. Soc.*, **87**, 5247 (1965).

(4) L. Petrakis and C. H. Sederholm, *J. Chem. Phys.*, **35**, 1243 (1961); S. Ng and C. H. Sederholm, *ibid.*, **40**, 2090 (1964); A. D. Cross, *J. Am. Chem. Soc.*, **86**, 4011 (1964); K. L. Servis and J. D. Roberts, *ibid.*, **87**, 1339 (1965).

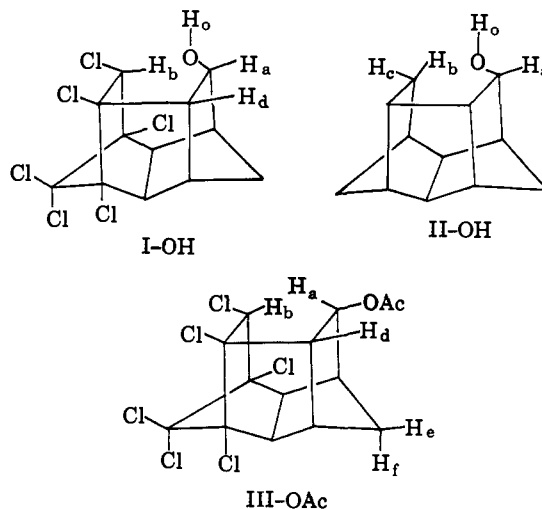
(5) S. B. Soloway, A. M. Damiana, J. W. Sims, H. Bluestone, and R. E. Lidov, *ibid.*, **82**, 5377 (1960).

(6) In valence-bond terms, this could occur as a result of a contribution of resonance structure IIIa to the resonance hybrid of III.



IIIa

(7) J. R. Holmes, D. Kivelson, and W. C. Drinkard, *J. Chem. Phys.*, **37**, 150 (1962).



larger with the chlorinated materials than with their unchlorinated counterparts. Thus,  $\Delta\delta$  is  $-2.0$  p.p.m. between III-OH and I-OH, while it may be estimated to be *ca.*  $-1$  p.p.m. with the unchlorinated alcohols.<sup>3</sup>

Regarding  $H_b$ - $H_o$  coupling in I-OH, the band of  $H_o$  in this compound is a well-resolved 1:1:1:1 quartet, with spacings of 4.8 and 1.1 c.p.s., while the band of  $H_b$  is a doublet, with a splitting of 1.1 c.p.s. It is therefore obvious that  $H_o$  is coupled to  $H_b$  by 1.1 c.p.s.<sup>8</sup> The various coupling constants between  $H_a$ ,  $H_b$ , and  $H_o$  are shown in Table I; decoupling experiments confirmed these assignments. The value of  $J_{ab}$  was estimated from the sharpening of the  $H_b$  doublet upon strong irradiation of  $H_a$ . With the unchlorinated II-OH at  $-20^\circ$  the band of  $H_o$  is a doublet ( $J_{ao} = 4.8$  c.p.s., line width = 0.9 c.p.s.). Therefore the value of  $J_{bo}$  is less than *ca.* 0.5 c.p.s.

Table I. Summary of Chemical Shifts and Coupling Constants

Compound	Solvent	Chem. shifts ( $\tau$ values)		
		$H_a$	$H_b$	$H_o$
I-OH <sup>a</sup>	Acetone	5.70	2.05	4.22 <sup>d</sup>
I-OH	CDCl <sub>3</sub>	5.83	2.60	
I-OAc	CDCl <sub>3</sub>	5.12	3.45	
II-OH <sup>b</sup>	Acetone	6.00	6.03	5.90 <sup>d,e</sup>
III-OH	CDCl <sub>3</sub>	5.05	4.60	
III-OAc <sup>c</sup>	CDCl <sub>3</sub>	4.20	4.52	

<sup>a</sup>  $J_{ad} = 5.5$ ,  $J_{ao} = 4.8$ ,  $J_{bo} = 1.1$ ,  $J_{ab} = 0.24$  c.p.s. <sup>b</sup>  $J_{ao} = 4.8$ ,  $J_{bo} < 0.5$  c.p.s. <sup>c</sup>  $J_{ab} < 1$  c.p.s. <sup>d</sup> Temperature dependent. <sup>e</sup> 5.4 p.p.m. at  $-20^\circ$ .

It is extremely unlikely that the coupling of  $H_b$  with either  $H_a$  or  $H_o$  proceeds by a through-bond mechanism, as the protons are separated by five and six single bonds, respectively.<sup>9</sup> Therefore the coupling most probably takes place *via* the unshared electrons of the oxygen atom. In both I-OH and II-OH one can consider the possibility that the  $H_b$ -O interaction partakes of the character of a hydrogen bond. Certain polyhalogenated hydrocarbons, *e.g.*, chloroform, are well known

(8) Not only is  $H_b$  coupled to  $H_o$ , but a "long-range" isotope effect (0.5 c.p.s. upfield) is observed for the chemical shift of  $H_b$  in I-OD. This isotope effect is rather remarkable in light of the fact that the isotope effects in CHD groups and in HDO<sup>7</sup> are only *ca.* 0.7 and 1.8 c.p.s., respectively.

(9) Coupling between OH and CH protons has not been reported even through four single bonds [S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964)].