University of Wisconsin Computing Center library subroutine UWHAUS which employs Marquardt's algorithm[37] to accomplish the fitting. The functional form was generally that of the sum of squares of two Gaussians so that there were five variable parameters to be determined.

Calculation of Enhancements in Region II. The calculation of $f_d(s)$ in the intermediate rate range began with the calculation of the average values of $r_{ij}(\Upsilon)^{-6}$ by a Simpson's rule integration of eq 13. The values of $\langle r_{ij}^{-6} \rangle$ are then used in place of the $\langle \rho_{ij} \rangle$ to solve eq 12 for $f_i(j)$ using the iterative procedure described above. The least-squares fits were accomplished in the same manner for region I and region II calculations.

Appendix II

Primary Geometries. Unsubstituted cyclopentanes and pentaheterocycles can exist in several formally distinct, low-energy conformational states in addition to the strained planar depiction.[38,39] Conceptually[40] these states are permutations around the ring of two basic geometric forms: the envelope, of C_s symmetry, in which one atom is out of the plane of the other four, and the half-chair, of C_2 symmetry, in which two atoms deviate from the plane of the other three, one above and one below.

Of the three parameters, the sugar ring puckering, the C-4′, C-5′ torsion angle, and the glycosyl torsion angle, that uniquely specify a nucleoside conformation, the glycosyl torsion angle is the strongest determinant of conformation dependent physical properties (*e.g.*, dipole moment, optical activity, etc.). First principles require that the C-4′ hydroxymethylene (C-5′, O-5′) substituent and the nucleobase be pseudoequatorial, thus creating a C_s form of tetrahydrofuran (with the ring oxygen puckered endo). In working with models, we express the relative disposition of these two substituents in terms of the corresponding H-1′, H-4′ distance. For a 2′,3′-dideoxy-β-ribonucleoside such a puckered conformation (O-1′ 0.4 Å endo) would relieve the intrinsic strain of the planar system. However, the ribose cis glycol acetonide favors a staggering of the oxygen atoms by analogy with the 2,2′-dimethyl-1,3-dioxolane system.[41] C-3′ 0.35 Å endo and an H-1′, H-4′ distance of about 3.0 Å (geometry III[A]) satisfy the requirements of the pseudoequatorial bulky substituents and of the skewed cis vicinal oxygens and are also consistent with the observed ribose coupling constants (Table VI). In comparison with others tested (see Table II) this geometry gives some of the best conformational fits[42] for NOE data on nucleoside 2′,3′-isopropylidene derivatives including the two discussed in this paper.

(37) D. W. Marquardt, *J. Soc. Ind. Appl. Math.*, 2, 421 (1963).
(38) K. Pitzer and W. Donath, *J. Amer. Chem. Soc.*, 81, 3213 (1959).
(39) R. Lemieux in "Molecular Rearrangements," Vol. 2, P. deMayo, Ed., Wiley-Interscience, New York, N. Y., 1964.
(40) L. Hall, P. Steiner, and C. Pedersen, *Can. J. Chem.*, 48, 1155 (1970), have suggested a very useful convention for denoting ribose geometry. For example, C-3′ 0.4 Å endo is ^{3}'V; C-3′ 0.4 Å exo is V$_3$'; C-3′ 0.2 Å endo, C-4′ 0.2 Å exo is ^{3}'T$_4$'; etc.
(41) R. Lemieux, J. Stevens, R. Fraser, *ibid.*, 40, 1955 (1962).
(42) J. P. Davis, unpublished experiments.

Halogen Substituent Effects on the Circular Dichroism of Pyrimidine Nucleosides. Nuclear Overhauser Effect and Circular Dichroism Correlations

Phillip A. Hart* and Jeffrey P. Davis

Contribution from the School of Pharmacy, University of Wisconsin, Madison, Wisconsin 53706. *Received July 9, 1971*

Abstract: On the basis of quantitative intramolecular nuclear Overhauser effects, 5-fluoro-, 5-chloro-, 5-bromo-, and 5-iodouridine are shown to be conformationally homogeneous in deuterium oxide and deuterated dimethyl sulfoxide (DMSO-d_6) or in mixtures of the two solvents. The ultraviolet spectra of the series vary with the halogen substituent transition moments, and the corresponding circular dichroism spectra evince a large influence of the 5-halogen substituent on the B_{2u} Cotton effect. Because of the conformational homogeneity of the series, differences in the circular dichroism spectra of the 5-halouridines in these solvents are attributed to direct electronic effects of the substituents.

The glycosyl torsion angle, Υ, of the pyrimidine ribonucleosides (see ref 1 for definition) is an important parameter in studies of RNA and t-RNA solution conformation.

Unusual pyrimidine nucleotide units characterized by rare aglycone substitution patterns appear in t-RNA's in particular[2] (*e.g.*, 4-thiouridine, 2-thiouridine, ψ-uridine). Some of these manifest the *syn*-glycosyl conformation in the solid state.[3] Knowledge of nucleobase substituent effects on nucleoside conformation in solution (particularly glycosyl conformation) is therefore of value.

Whereas pyrimidine nucleosides have generally been thought to assume the anti conformation in solution (**1**, Figure 1), we have unequivocally established the glycosyl conformation of 2′,3′-isopropylideneuridine in DMSO

(1) R. E. Schirmer, J. P. Davis, J. H. Noggle, and P. A. Hart, *J. Amer. Chem. Soc.*, 94, 2561 (1972).
(2) K. Miura, *Progr. Nucl. Acid Res. Mol. Biol.*, 5, 39 (1967).
(3) W. Saenger and K. Scheit, *Angew. Chem., Int. Ed. Engl.*, 8, 139 (1969).

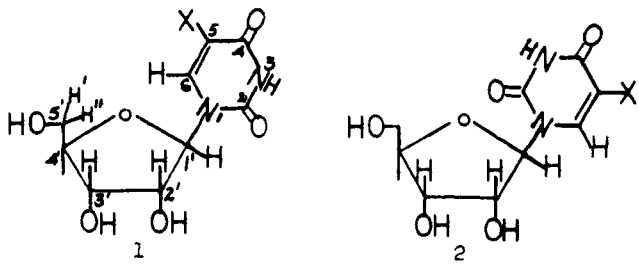

Figure 1. Syn and anti glycosyl conformers of 5-halouridine.

to be syn.[4] This observation, in addition to above-mentioned X-ray data for 4-thiouridine, is evidence for the perturbation of the glycosyl conformation by subtle environmental and structural factors. We have therefore undertaken to characterize several of these factors. This report details the effects of 5-halogen substitution on pyrimidine riboside glycosyl conformation as determined by quantitative application of the nuclear Overhauser effect and correlates the determined conformations with circular dichroism spectra.

Experimental Section

5-Fluorouridine (5-FUR), a product of Hoffmann-La Roche, was a gift of Professor Charles Heidelberger. A-Grade 5-iodouridine (5-IUR) and 5-chlorouridine (5-ClUR) were purchased from Calbiochem. 5-Bromouridine (5-BrUr) was obtained from Sigma Chemical Co. Samples were dried for 12 hr at 60° under 5 mm of pressure before use for either nuclear magnetic resonance (nmr), ultraviolet (uv), or circular dichroism (CD) measurements.

CD measurements were made on a Cary 60 recording spectropolarimeter fitted with a Model 6002 CD attachment, with the slit programmed for a half-bandwidth of 15 Å. Measurements were made at path lengths ranging from 0.1 to 1 cm and for concentrations between 10^{-3} and 10^{-4} *M*. The low-wavelength region of the spectrum was inaccessible for the DMSO solutions because of high solvent absorbance below *ca.* 250 nm. The CD is recorded as molecular ellipticity, $[\theta]$, in units of degree square centimeter per decimole, and absorbances never exceeded 2. The solutions were not buffered so that ionic strength factors would not enter the NOE–CD comparisons. The resultant pH uncertainties are probably not severe. The instrument was calibrated using (+)-camphorsulfonic acid (Aldrich).

Ultraviolet absorption spectra were taken on a Cary 14 recording spectrophotometer in cells of 0.1–5.0-cm path length. All uv and CD spectra in DMSO were run in a 0.1-cm cell.

Chemical shifts were derived from nmr spectra taken on a Varian A 60-A spectrometer. Pyridine-d_5 and DMSO-d_6 were from Merck Sharpe and Dohme and D_2O was purchased from Diaprep, Inc. The NOE experiments were done in coaxial tubes on a Varian HA-100 nmr spectrometer as previously described.[5]

It was shown that peak-height changes correspond well with peak area changes. The symbol $f_m(n)$ used to report the NOE data denotes here the fractional enhancement of the resonance *m* upon irradiation of resonance *n*.

Plots of NOE *vs.* the glycosyl torsion angle, Υ, calculated for range I glycosyl conformation exchange rate[6] are included (see Figures 2 and 3). Υ is defined in ref 1.

Where the H-4′ resonance overlapped another which was irradiated the results are reported as such. It is apparent from Figure 2 that saturation of H-4′ yields no enhancements greater or less than zero by more than the experimental error, $\sigma \approx 0.03$, even in the anti conformation. Simultaneous irradiation of H-4′ and another resonance is thus, for practical purposes, innocuous. Nmr solvent mixtures are reported as per cent by volume before mixing. Computer fits of NOE data were performed for two glycosyl rotation rates,[1] range I, $k < 1$ sec^{-1}, and range II, 1 sec^{-1} $< k <$ 10^9 sec^{-1}.

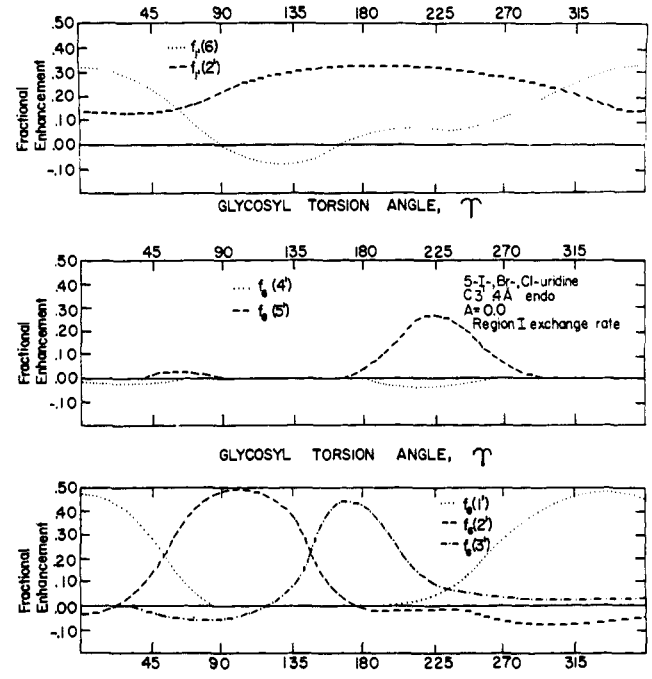

Figure 2. Plots of calculated nuclear Overhauser effects in 5-chloro-, 5-bromo-, and 5-iodouridine with a C-3′ endo ribose as a function of glycosyl torsion angle.

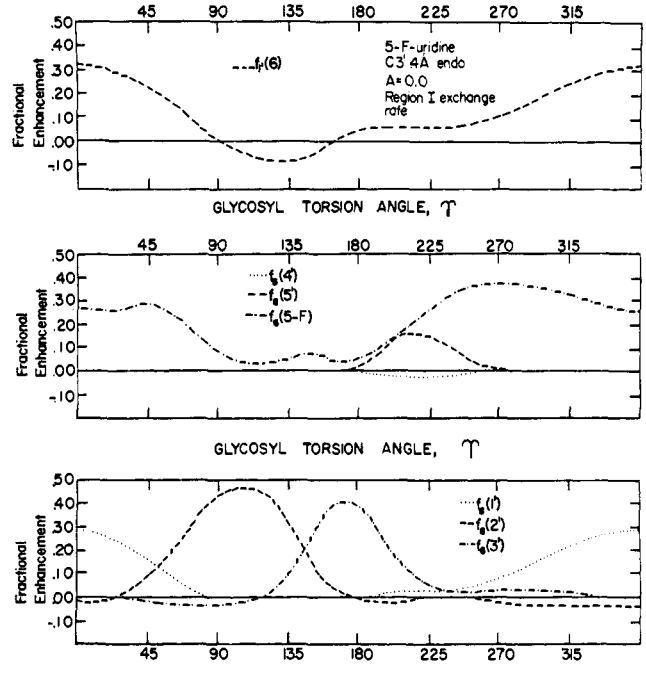

Figure 3. Plots of calculated nuclear Overhauser effects in 5-fluorouridine with a C-3′ endo ribose as a function of glycosyl torsion angle.

Of the various possible combinations of glycosyl rotation rate, ribose conformation, and intermolecular relaxation correction, the generally best combination for all sets of data by the sum of squares[7] criterion of goodness of fit was the slow-exchange limit, zero intermolecular relaxation correction, and a ribose conformation described below. Models on which the NOE calculations were based[8] were Framework Molecular Models constructed using bond lengths

(4) P. A. Hart and J. P. Davis, *J. Amer. Chem. Soc.*, **93**, 753 (1971); see also ref 1.
(5) P. A. Hart and J. P. Davis, *ibid.*, **91**, 512 (1969).
(6) See ref 1.
(7) See ref 1 for discussion of the criterion of goodness of fit.
(8) See ref 1 for a thorough description of the method.

Table I. Ribose Proton Spin-Coupling Constants

Nucleoside	Solvent	$J_{1',2'}$, Hz
5-FUR	DMSO-d_6	4.0
	D_2O	4.0
5-ClUR	DMSO-d_6	3.8
	50% D_2O in DMSO[a]	3.8
5-BrUR	DMSO-d_6	4.0
	D_2O	3.3
5-IUR	DMSO-d_6	4.0
	16% D_2O in DMSO-d_6[a]	4.0
UR	DMSO	4.6
	25% pyr-d_5 in D_2O[a]	3.2

[a] Mixed solvents are reported as volume per cent before mixing. The proportion of D_2O was made as large as possible without precipitating the nucleoside.

The ribose conformation which gave the generally best fit for all eight sets of NOE data was $^3'T_{2'}$. Calculations on the C-5-fluoro compound were done including the fluorine nucleus and using the standard hydrogen magnetogyric ratio,[12] γ, of 1.0 and a fluorine γ of 0.94.

The final glycosyl conformer distributions obtained in ranges I and II were quite similar. The fact that range I fits usually had smaller sums of squares suggests that the rate of rotation about the glycosyl bond in 5-halouridine is slower than in some other pyrimidine nucleosides.[13]

Results

The H-1′, H-2′ first-order spin-coupling constants ($J_{1',2'}$) of the halouridines in both solvents are uniformly close to 4.0 Hz (Table I), while the same coupling constant of uridine is slightly more solvent dependent but still near 4.0 Hz (Table I). This J value is consistent with an H-1′, H-2′ dihedral angle greater than 90°, which would obtain in a C-3′ endo conformation. The solvent insensitivity of $J_{1',2'}$ typifies a solvent-independent sugar conformation. The ribose proton chemical

Table II. Ribose and Nucleobase Chemical Shifts[a]

Nucleoside	Solvent	1′	2′, 4′	3′	5′	5	6
5-FUR	DMSO-d_6	6.20	4.45	4.34	4.08		8.75
	D_2O	6.43	4.79	4.67	4.41		8.64
5-ClUR	DMSO-d_6	6.19	4.43	4.35	4.06		8.84
	D_2O–DMSO-d_6[b,d]	6.30	4.58	4.46	4.18		8.78
5-BrUR	DMSO-d_6	6.18	4.43	4.35	4.06		8.85
	D_2O	6.38	4.79	4.66	4.41		8.86
5-IUR	DMSO-d_6	6.15	4.43	4.34	4.06		8.90
	D_2O–DMSO-d_6[c,d]	6.24	4.50	4.43	4.15		8.94
i-UR	DMSO-d_6	6.20	5.28, 4.43[e]	5.12	3.96	6.00	8.20
	D_2O–DMSO-d_6[b]	6.32	5.44, 4.70[e]	5.26	4.16	6.24	8.24
UR	DMSO-d_6	6.12	4.36	4.23	3.95	5.99	8.22
	D_2O	6.34	*f*	*f*	4.33	6.36	8.24

[a] Reported in units of δ, parts per million from an internal TMS capillary. No bulk susceptibility corrections were made. 0.25 *M* nucleoside. [b] 50% D_2O–DMSO-d_6. [c] 16% D_2O–DMSO-d_6. [d] Volume per cent before mixing. Proportion of D_2O as large as possible without causing precipitation. [e] Chemical shift of the distinct H-4′ resonance. [f] Difficult to measure owing to overlap.

Table III. Observed Nuclear Overhauser Effects[a]

	$f_6(1')$	$f_6(2')$[b]	$f_6(3')$	$f_6(5')$	$f_6(1')$	$f_6(2')$	$f_6(3')$	$f_6(5')$
5-IUR	0.07[c]	0.27[c]	0.07[c]	0.0	0.03	0.27	0.17	0.05
5-BrUR	0.07	0.24	0.17	0.06	0.06	0.32	0.26	0.13
5-ClUR	0.06[d]	0.32[d]	0.30[d]	0.16	0.07	0.24	0.14	0.07
5-FUR	0.07	0.22	0.20	0.12	0.0	0.20	0.16	0.08

[a] 0.25 *M* nucleoside. [b] Includes irradiation of H-4′ in some cases; see Table II. [c] 16% v/v D_2O in DMSO-d_6. [d] 50% v/v D_2O in DMSO-d_6.

Table IV. Ultraviolet Absorption and Circular Dichroism Data for the B_{2u} Band of the 5-Halouridine Series[a] and Uridine

	H_2O				DMSO			
	CD λ_{max}, nm	$[\theta]_{max} \times 10^{-3}$	Uv λ_{max}, nm	$\epsilon_{max} \times 10^{-4}$	CD λ_{max}, nm	$[\theta]_{max} \times 10^{-3}$	Uv λ_{max}, nm	$\epsilon_{max} \times 10^{-4}$
5-FUR	273	8.19	268	1.10	277.5	13.9	271	0.842
5-ClUR	282.5	4.94	276	1.26	287	7.65	277.5	0.920
5-BrUR	287.5	3.30	279	1.08	288	6.32	280	0.888
5-IUR	298	−0.91	287	0.792	285	−1.39	287.5	0.802
	273	+0.91			273	−0.90		
U	267[b]	8.50	268[c]	1.40	277[a]	10.1	264[a]	0.945

[a] This work. [b] D. W. Miles, M. J. Robins, R. K. Robins, M. W. Winkley, and H. Eyring, *J. Amer. Chem. Soc.*, **91**, 824 (1969). [c] D. W. Miles, R. K. Robins, and H. Eyring, *Proc. Nat. Acad. Sci. U. S.*, **57**, 1138 (1967).

from published X-ray structures.[9] Conventional bond angles were used. A $^3'T_{2'}$ (C-3′ endo, C-2′ exo) or $^3'V$ (C-3′ endo) conformation[10] is qualitatively indicated by the large experimental enhancements, $f_6(3')$. A total analysis of the ribose first-order coupling constants is not possible because of the poorly resolved couplings. $^3'T_{2'}$ and $^3'V$ ribose conformations give practically indistinguishable computer fits. No other ribose geometries can result in such large $f_6(3')$'s for any glycosyl conformation.[11]

(9) For example, J. Iball, C. Morgan, and H. Wilson, *Proc. Roy. Soc., Ser. A.*, 295 (1966).

(10) According to the *T*wist and *E*nvelope pentacycle conformation convention of L. Hall, P. Steiner, and C. Pedersen, *Can. J. Chem.*, **48**, 1155 (1970).

(11) Unpublished calculations of J. P. Davis.

(12) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959.

(13) For example 2′,3′-isopropylideneuridine, which is fit slightly better in range II than in range I; see ref 1.

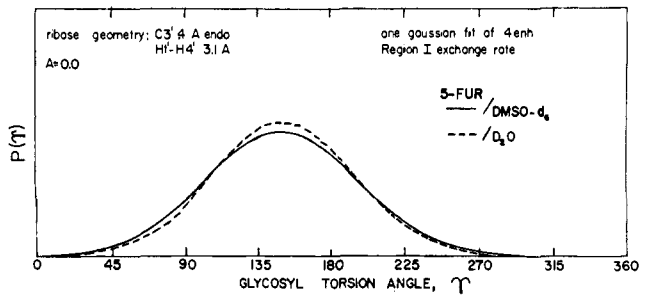

Figure 4. Computer fits of glycosyl conformational distributions to experimental nuclear Overhauser effects (Table III) in the 5-halouridines.

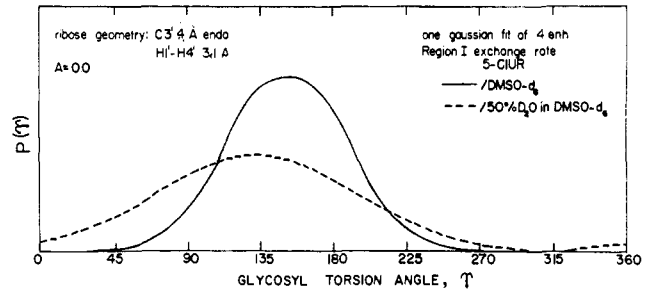

Figure 5. Computer fits of glycosyl conformational distributions (see caption of Figure 4).

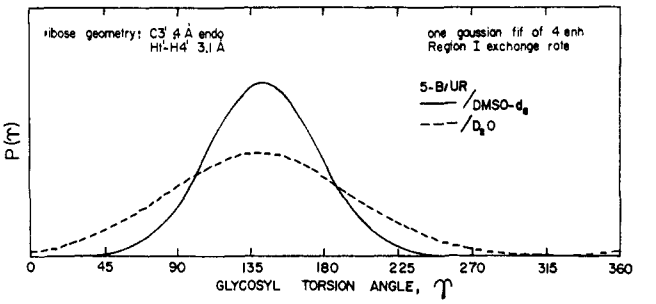

Figure 6. Computer fits of glycosyl conformational distributions (see caption of Figure 4).

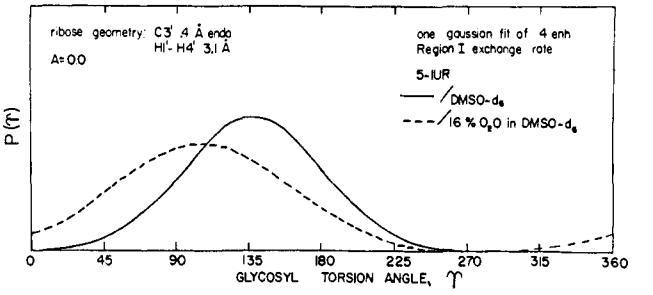

Figure 7. Computer fits of glycosyl conformational distributions (see caption of Figure 4).

shifts in the 5-substituted uridines (Table II) generally shift downfield in D_2O relative to DMSO and exhibit little sensitivity to the identity of the halogen substituent. H-6 in the 5-halouridines is shifted upfield in water relative to DMSO or is insensitive to solvent.

A moderate downfield shift of H-6 is occasioned by substitution of halogen for hydrogen at C-5 in the same solvent (Table II). This is the direction of change expected on electronic grounds alone for the chemical shift of a vicinal proton on a double bond cis to the point of successive α-F, Cl, Br, I substitution.[14]

The glycosyl conformer probability distributions (Figures 4–7) fitted to the observed NOE's (Table III) denote glycosyl torsion angles in the anti range for all the 5-halopyrimidine ribosides. The fitted widths should be considered qualitative indicators of the relative breadth of the distributions. The computer fits for fluorouridine are consistent with conclusions reached by Cushley, *et al.*,[15] on the basis of long-range proton–fluorine spin-coupling-constant analysis.

The 5-halouridine series gives ultraviolet spectra whose maximum absorbances associated with the B_{2u} band are responsive to the nature of substituent at the 5 position (Table IV), apparently shifting to longer wavelengths as the list F, Cl, Br, I is traversed. The B_{2u} extinction coefficients (ϵ's) for the F, Cl, and Br compounds are 20–30% higher in water than in DMSO, and the large value for the chloro compound is outstanding in what otherwise might be a substituent insensitivity among the three nucleosides. The iodo compound requires special consideration since its $\Delta\epsilon_{DMSO-H_2O}$ is positive, while for the other compounds in the series $\Delta\epsilon_{DMSO-H_2O}$ is negative. The CD behavior of 5-IUR in the B_{2u} region is also unexpected (Figures 8 and 9). The different optical behavior of 5-IUR in water and DMSO seems to be reflected in the observation that in DMSO it gives a single, apparently conventional B_{2u} CD curve (albeit with an unexpectedly low ellipticity) and in water elicits an apparently split band, or an entirely new one. The water CD spectrum of 5-IUR is not sensitive to concentration over the range 2.02×10^{-3}–4.1×10^{-5} *M*.

Vapor pressure osmometry (vpo) examination of 5-IUR in water gave no indication of self-association up to 0.1 *M*. No vpo measurements were made beyond that concentration, and none was made in DMSO because of that solvent's unworkably low vapor pressure.

The shapes of the CD curves of the other three nucleosides in DMSO and water are similar but for a magnified ellipticity in DMSO. The B_{2u} molecular ellipticity decreases in the order 5-fluoro-, 5-chloro-, 5-bromo-, and 5-iodouridine and is roughly half as great for the fluoro, chloro, and bromo cases in water as it is in DMSO (see Table IV and Figures 8 and 9).

Discussion

The determinants of the solution glycosyl conformation of the 5-halouridines must be subtle. The consistent anti-like conformations seen for this series contrast with the syn conformation seen for isopropylideneuridine[1] and the intermediate conformation of uridine evident from an intuitive interpretation of its NOE's (Table III).

The magnitudes of the NOE's of uridine should be compared with those of other 5-H pyrimidine nucleosides and not with the 5-X derivatives. Comparison of the relative ribose–nucleobase proton NOE's within one nucleoside to those in another gives a qualitative idea of the relative glycosyl conformations of the 5-H

(14) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," International Series of Monographs in Organic Chemistry, Vol. 5, 2nd ed, Pergamon Press, Elmsford N. Y., 1969, p 184.

(15) R. J. Cushley, I. Wempen, and J. J. Fox, *J. Amer. Chem. Soc.*, 90, 709 (1968).

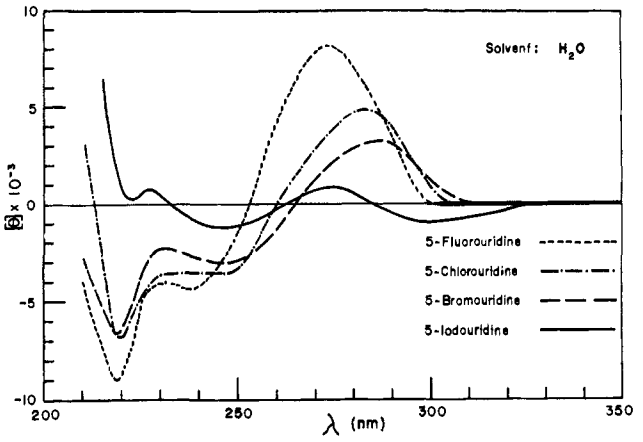

Figure 8. Circular dichroism spectra of 5-fluoro-, 5-chloro-, 5-bromo-, and 5-iodouridine in water.

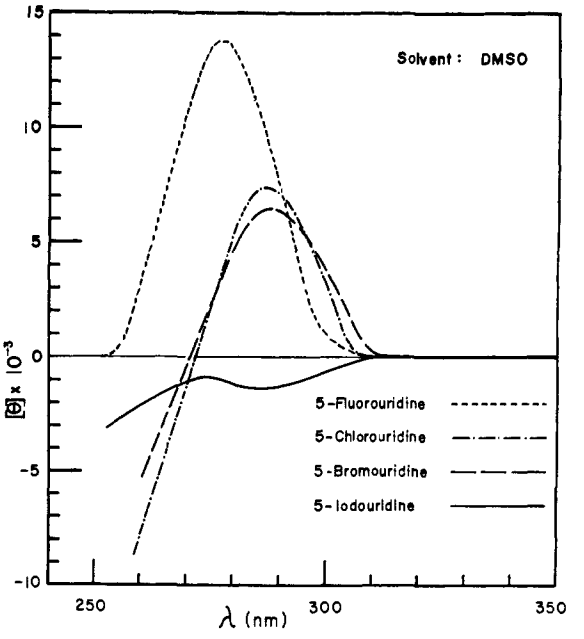

Figure 9. Circular dichroism spectra of 5-fluoro-, 5-chloro-, 5-bromo-, and 5-iodouridine in dimethyl sulfoxide.

and 5-X derivatives. $f_6(1')$ is generally smaller for the 5-H derivatives (Table III) because of the strong interaction of H-5 with H-6. The uridine case cannot be analyzed rigorously because the H-2′ and H-3′ resonances coincide, but it likely exists in either a mixture of the syn and anti conformers or has a single preferred conformation in the Υ = 90–100° range. How the 5-halo substituent might account for the greater weight of the anti conformer in the 5-halouridine systems is not immediately evident, although solvent-dependent dipolar interactions between the base and the sugar might account for the stability of the anti conformer in the 5-halouridines. In the absence of dipole moment calculations as a function of glycosyl torsion angle, speculation is futile.

Regardless of the rationale, the NOE experiments show a clear preference of the 5-halouridines for the anti conformation (Υ = 100–200°) about the glycosyl bond under the conditions specified here. Thus, this series is conformationally homogeneous. The following discussion of CD data is in light of this fact.

The observed molecular ellipticities are instructive along several lines. First, the trend from the fluoro to the iodo compound is toward smaller ellipticities. This trend must be due exclusively to an electronic effect rather than to any substituent mediated conformational change. For the uniform glycosyl conformation of the series studied here, the intrinsic ellipticities of each of the 5-halouridines are different, and it is clear that CD comparisons alone among the 5-halouracil ribosides are inadequate criteria of their exact glycosyl torsion angles. Iodouridine may be a special case and is further considered.

The iodouridine CD spectrum in water is complex. The same apparent splitting exists in the aqueous 5-iodo-2′-deoxyuridine CD spectrum, though not to the same extent as in the riboside. No such complexity is observed in the spectrum of 5-iodo-2′-deoxycytidine.[16] The two long-wavelength CD extrema of 5-IUR in water (298 and 273 nm) flanking the ultraviolet maximum (287 nm) might arise from exciton coupling or from the summation of the B_{2u} band and a new optically active transition, perhaps an oxygen n–π^* band or the iodine n–σ^* band. The splitting apparently does not arise from intermolecular association, because 5-iodouridine solutions are ideal up to 0.1 *M* according to vapor pressure osmometric analysis and because the CD spectrum is independent of concentration. In contrast, the approximate agreement of the wavelength of maximum ellipticity and maximum absorbance in the long-wavelength region in DMSO suggests that the long-wavelength negative Cotton effect in that solvent arises from a single band.

Miles, Robins, and Eyring[17] have used the substituent transition moment[18] (Table V) in a discussion of substituent effects on optical activity in the purine nucleoside series and have observed that C-6 substituents decrease the amplitude of the B_{2u} ellipticity. Whether ellipticity is more directly related to substituent polarizability than to the transition moment in this series might be determined by calculations of the type recently applied to nucleoside circular dichroism.[19]

Table V. Substituent Transition Moments and Group Polarizabilities

Substituent	Group, polarizability,[a] 10^{-24} cm^3	Transition, moment,[b] $q \times 10^{10}$
F	0.38	12.5
Cl	2.28	6.0
Br	3.34	6.0
I	5.11	8.0
H	0.24	

[a] From J. A. A. Ketelaar, "Chemical Constitution, An Introduction to the Theory of the Chemical Bond," Van Nostrand, Princeton, N. J., 1958, p 91. [b] From J. Petruska, *J. Chem. Phys.*, **34**, 1120 (1961).

(16) D. W. Miles, M. J. Robins, R. K. Robins, M. W. Winkley, and H. Eyring, *J. Amer. Chem. Soc.*, 91, 831 (1969).

(17) D. W. Miles, R. K. Robins, and H. Eyring, *J. Phys. Chem.*, 71, 3931 (1967).

(18) J. Petruska, *J. Chem. Phys.*, **34**, 1111 (1961), and references therein.

(19) (a) W. H. Inskeep, D. W. Miles, and H. Eyring, *J. Amer. Chem. Soc.*, **92**, 3866 (1970); (b) D. W. Miles, W. H. Inskeep, M. J. Robins, M. W. Winkley, R. K. Robins, and H. Eyring, *ibid.*, **92**, 3872 (1970).

Another point deriving from the CD experiments is the near doubling of the nucleoside B_{2u} molecular ellipticities in DMSO relative to water (Figures 8 and 9). Although the carbonyl chromophore is far less complex than the pyrimidine chromophore at issue here, the same hypothesis offered to explain anomalous solvent effects on chiroptical spectra of some selected ketones[20] may be involved in the DMSO solvent effect on the present 5-halouridine ellipticities. Kirk, Klyne, and Wallis suggested two general solvent effects: (1) changes in perturbation of the chromophore by asymmetric solvation and (2) solvent-dependent vicinal effects. In the present case, an additional phenomenon must be considered, (3) induced optical activity of the solvent. This last is plausible for DMSO because its absorption maximum[21] is in the vicinity of the pyrimidine B_{2u} transition. Although the contribution to the total molecular ellipticity by an extrinsic DMSO Cotton effect induced by specific nucleoside binding is an intriguing possibility, there is no evidence that allows either its rejection or acceptance. In view of the conclusion that the conformations of the series in water and in DMSO are quite similar, the second possibility is of minor importance. Thus solvational change without significant conformational change is implicated.

(20) D. N. Kirk, W. Klyne, and S. R. Wallis, *J. Chem. Soc. C*, 350 (1970).
(21) U. Quintily and G. Scorrano, *J. Chem. Soc. D*, 260 (1971).

Little differential H_2O–DMSO solvent effect is seen on the ellipticity of syn nucleosides,[4] and only a moderate enhancement of the uridine ellipticity is seen on going from H_2O to DMSO solvent (Table IV). If, as noted above, uridine may be characterized by some proportion of the anti conformer, the DMSO ellipticity enhancement may be operative in proportion to the amount of anti conformer present.

Conclusion

The important result of this work is the separation of substituent from conformational effects on the CD of a series of nucleosides by means of an independent and more intimate probe, the nuclear Overhauser effect. Future work will be directed toward more extensive characterization of substituent effects.

Acknowledgment. Financial support of this work was provided by the Wisconsin Alumni Research Foundation and by a National Institutes of Health General Research Support Grant. The assistance of Richard A. Wood and the National Science Foundation Undergraduate Research program that supported him is acknowledged. We thank the University of Wisconsin Chemistry department for use of the HA-100 spectrometer. The sample of 5-fluorouridine was graciously supplied by Professor Charles Heidelberger.

Vapor-Phase Charge-Transfer Complexes. VII. Iodine Complexes with Diethyl Sulfide and Dimethyl Sulfide[1]

Milton Tamres* and S. N. Bhat

Contribution from the Chemistry Department, University of Michigan, Ann Arbor, Michigan 48104. *Received July 19, 1971*

Abstract: A spectrophotometric study in the vapor phase of the dimethyl sulfide–iodine and diethyl sulfide–iodine complexes has been made. The equilibrium constants are lower and the oscillator strengths of the charge-transfer bands are higher than previously reported in the literature. In comparison with solution data, these results indicate a smaller solvent influence than had been believed. Further, the relative oscillator strengths of these two complexes are found to follow their relative strengths of complexation, in contrast to an earlier report. The blue-shifted iodine band for dimethyl sulfide–iodine in the vapor phase also has been characterized.

Sulfides are relatively strong donors toward iodine, and the complexes formed have CT bands located in a region comparatively clear of absorbance by the components. These are desirable characteristics for spectrophotometric study, particularly in the vapor phase, where the concentration range is necessarily small because of pressure limitations.[2]

Results from two laboratories on the vapor-phase study of diethyl sulfide–iodine[3-5] are in agreement on the $K_c\epsilon_{max}$ product (*i.e.*, equilibrium constant times extinction coefficient at λ_{max}). However, they differ in the separated K_c and ϵ_{max} values by a factor of $\sim$3.5. This is rather disconcerting, considering that this system ought to be among the more favorable ones to study. Resolving this difference is important in order to determine the extent of solvent influence on these properties when comparison is made with solution data. Further, as has been reported, a reliable value for K_c is needed for characterization of the blue-shifted iodine band.[6]

(1) Presented before the Division of Physical Chemistry at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 28–April 2, 1971.
(2) R. A. LaBudde and M. Tamres, *J. Phys. Chem.*, **74**, 4009 (1970).
(3) J. M. Goodenow and M. Tamres, *J. Chem. Phys.*, **43**, 3393 (1965).
(4) M. Tamres and J. M. Goodenow, *J. Phys. Chem.*, **71**, 1982 (1967).
(5) M. Kroll, *J. Amer. Chem. Soc.*, **90**, 1097 (1968).
(6) M. Tamres and S. N. Bhat, *J. Phys. Chem.*, **75**, 1057 (1971).