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β-UREIDO ACIDS AND DIHYDROURACILS—VII[1]

APPLICATIONS OF PROTON RESONANCE SPECTROSCOPY—XXXII;[2] NMR SPECTRA AND CONFORMATION OF DIHYDROURACILS AND RELATED COMPOUNDS

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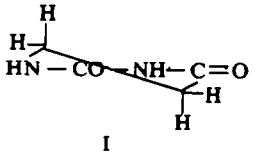
Abstract—The NMR spectra of the *cis* and *trans*-isomers of 5,6-tetramethylenedihydrouracil (2,4-dioxodecahydroquinazoline, TMDHU), 5,6-dimethyldihydrouracil (DMeDHU), 5,6-diphenyldihydrouracil (DPhDHU), 5-methyldihydroorotic acid (MeDHO), as well as those of dihydroorotic acid (DHO) and its methyl ester, and 6-phenyldihydrouracil (PhDHU) are reported. The J_{trans} and J_{16} coupling constants of these and other dihydrouracils are used in the conformational analysis. Contrary to earlier suggestions[3,4] of widely varying distortion of the dihydrouracil ring, the variation of *cis* J_{56} and J_{16} is best explained by electronegativity and equilibrium effects. Carboxy and methoxycarbonyl groups at C-6 prefer the axial orientation. A phenyl group at C-6, and the two phenyls in *trans*-DPhDHU, are predominantly axial in dimethyl sulphoxide, but equatorial in trifluoroacetic acid.

The coupling constants of the *cis* and *trans* isomers of 2-ureidocyclohexane carboxylic (UCHA) and of the *erytho* and *threo* isomers of 2-methyl-3-ureidobutyric acid (MeUBA) and of 2,3-diphenyl-3-ureidopropionic acid (DPhUPA) indicate that with both isomers of MeUBA conformers with gauche hydrogens are preferred, while in the case of DPhUPA *trans* hydrogens predominate.

DIHYDROURACILS are of great biological interest; they occur as minor bases in some DNA,[5] and ionising radiation and important mutagenic reactions convert the normal pyrimidine bases into such derivatives. This class of compound has been extensively studied at Sofia and, in particular, rate differences for the ring-opening[6,7] of dihydrouracils and equilibration studies interpreted in terms of a distorted half-chair conformation I for the DHU ring, and by the NMR results now described. Little previous work has appeared on the conformation of the DHU ring apart from that of Nofre *et al.* on IR[8] and NMR spectra.[3,4,9] From the IR work[8] it was concluded that the dihydrouracil ring has a distorted half-chair conformation, since 5-halo derivatives showed shifts of the C=O stretching frequency similar to α-halocyclohexanones. It was further claimed[8] that bands could be assigned to the separate axial and equatorial ν(C—OH) allowing conclusions regarding the relative amounts of the two conformers to be made from their relative intensities. However, the determinations were affected in *KBr discs* and we cannot agree that this "devrait être suffisante pour mener à bien une analyse préliminaire"; most crystals contain only one conformer. The NMR papers[3,4,9] appeared during the course of the present work; as discussed below we agree with most of their conclusions. Our own work extends and generalises the treatment; it includes in particular the important model

compounds *cis*-(II) and *trans*-5,6-tetramethylenedihydrouracil (III). The assumption of a half-chair conformation of the DHU ring has recently been confirmed by X-ray analysis.[10]

β-Ureido acids and Dihydrouracils



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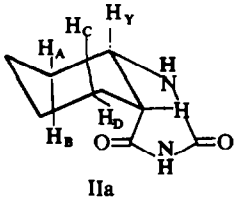
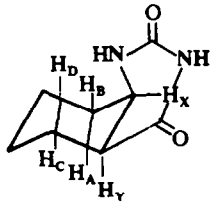


IIa



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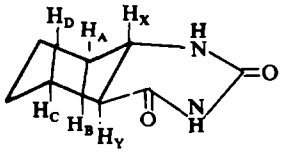

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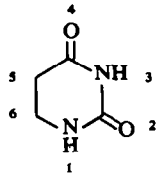

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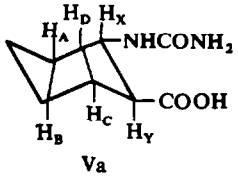
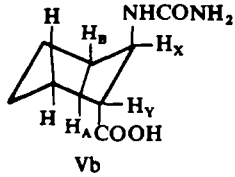


Va

NH_MCONH_2



Vb

EXPERIMENTAL

Materials. The following compounds were prepared by the literature methods quoted. Ref. 11: *erythro*- and *threo*-2-methyl-3-ureidobutyric acid and their methyl esters, *erythro*- and *threo*-2,3-diphenyl-3-ureidopropionic acid and their methyl esters, *cis*- and *trans*-5,6-dimethyldihydrouracil and *trans*-5,6-diphenyldihydrouracil. Ref. 1: *cis*-5,6-diphenyldihydrouracil. Ref. 12: *cis*- and *trans*-2-ureidocyclohexane carboxylic acid and *cis*- and *trans*-5,6-tetramethylenedihydrouracil. Ref. 13: 3-phenyl-3-ureidopropionic acid and 6-phenyldihydrouracil.

Methyl ester of dihydroorotic acid. Hydrogenation of methyl orotate[14] (1 g) in MeOH (250 ml) over

PtO_2 (0·8 g) at 80 atm and 100–120° for 8 hr[15] gave *methyl dihydroorotate* (70%) as needles, m.p. 198–200° (twice from MeOH). (Found: N, 16·64. $C_6H_8N_2O_4$ requires: N, 16·28%).

cis- and *trans*-5-Methyldihydroorotic acid were kindly supplied by Dr. J. Reid and Dr. M. Atcheson (University of Surrey).

Spectra. Spectra at 60 Mc/s were recorded on a Perkin–Elmer R 10 or a Jeol C-60S spectrometer at ambient temp. Line positions and separations are averages of several up and downfield sweeps and were reproducible to 0·2 c/s. Spectra at 100 Mc/s were obtained on a Varian HA 100 spectrometer at 33 ±2°. Concentrations (unless otherwise stated) were 0·5 to 0·8 M. Tetramethylsilane, sodium 3-trimethylsilylpropane-1-sulphonate (both $\tau = 10$ ppm), or tetramethylammonium sulphate ($\tau = 6{\cdot}80$ ppm) were used as an internal reference. Double irradiation utilised a Muirhead low frequency decade generator, with errors not exceeding ±0·2 c/s in the coupling constants unless otherwise stated.

For most DHU derivatives, formamide proved a satisfactory solvent in which the stereochemically important H—N(1)—C(6)—H coupling could be observed. Where solubility in this solvent was insufficient, DMSO sulphoxide or trifluoroacetic acid were used. MeUBA and their esters were studied in D_2O, since their conformations in aqueous soln are of particular interest; for the Ph substituted derivatives this was not feasible because of low solubility.

RESULTS

Chemical shift and coupling constant data are summarized in Tables 1 to 6. Most spectra were sufficiently first order to allow direct determination of coupling constants from observed splittings and band widths. However, the methine multiplets of the Me substituted derivatives showed second-order splitting due to the CH_3–CH coupling and the coupling constants were abstracted by a trial and error adjustment using tabulated data for the part AB_3 case.[16] The HN–CH coupling was observed in DMSO and in formamide; it collapsed on the addition of ca. 10% of trifluoroacetic acid. Long range coupling of H-1 or -3 with H-5 in the DHU derivatives, reported in Ref. 4, due to resolution or solvents used, was observed unambiguously only in the case of the methyl ester of DHO in DMSO (the coupling across four bands of H-5e to both H-1 and H-3 was ca. 0·2 c/s). In the mono-substituted dihydrouracils, the ring CH_2CH resonances were analysed as ABX systems. The values for DHO in deuterium oxide (Table 2) are based on analysis of the well-defined AB part of an ABX arising from the C-5 protons; the X multiplet from H-6 was buried in the lock signal (H_2O): the value $\frac{1}{2}|J_{AX} + J_{BX}|$ of 6·0 was taken from the separation of the midpoints of the two quartets. In formamide, the H-6 multiplet of DHO appears as a sextet analysing for $J_{16} = 3{\cdot}0$ c/s and $J_{56} + J_{5'6} = 12{\cdot}2$ c/s; addition of trifluoroacetic acid collapsed the sextet to a poorly resolved triplet with outer-line separation of ca. 12 c/s. Solubility in formamide is low and the weaker lines of the H-5 multiplet were lost in the noise.

The NMR spectrum of PhDHU, previously[4] described as giving the C(5)H_2C(6)H resonances as an AX_2 with $J_{16} = 8{\cdot}2$ c/s, was an exception to the results obtained. This single example of J_{16} of this magnitude in a series of dihydrouracils, designated[4] as "cas particuliér", casts doubt on the validity of conformer conclusions based on J_{16} values (*vide infra*), at least when applied to Ph-substituted DHU. The spectrum of PhDHU in DMSO-d_6 was therefore re-examined. The expected ABX pattern for the C(6)H_2C(5)H resonances was observed but with $J_{16} = 2{\cdot}6$ c/s. Our spectrum of 3-phenyl-3-ureido propionic acid (PhUPA) in DMSO-d_6, corresponds closely to that previously[4] described for PhDHU and apparently an error in compounds is involved.[17] The following chemical shifts in τ values against TMS and coupling constants in c/s were obtained for a solution of PhUPA (56 mg) in DMSO-d_6 (0·40 ml), (the values in brackets are those of Ref. 4 for PhDHU):

TABLE 1. NMR SPECTRA OF 5,6-SUBSTITUTED DIHYDROURACILS

Substituents			Solvent	Mc/s	Chemical shifts (τ)				Coupling constants (c/s)			
5	6	Config.			Me_5	Me_6	H_5	H_6	$J_{H_5H_6}$	$J_{H_5Me_5}$	$J_{H_6Me_6}$	$J_{H_1H_6}$
Me	Me	*cis*	DMSO-d_6[a]	60	8·99	9·00	7·35	6·45	5·1	7·05	6·5	3·1
			$HNCONH_2$	60	8·83	8·83	7·18	6·22	5·2	7·0	6·6	3·0
				100	8·83	8·83	7·20	6·27	5·2	7·2	6·6	2·9
Me	Me	*trans*	DMSO-d_6[a]	60	8·94	8·87	7·78	6·76	9·5	6·8	6·3	~1·5
			$HCONH_2$	60	8·79	8·70	7·60	6·56	10·2	6·9	6·0	~1
				100	8·79	8·70	7·57	6·54	10·1	6·9	6·3	~1
Me	COOH	*cis*	1:1 $HCONH_2$:D_2O	100	8·79	—	6·91	—	5·75	7·15	—	—
			$HCONH_2$	100	8·76	—	6·86	5·59	6·05	7·1	—	3·2
Me	COOH	*trans*	1:1 $HCONH_2$:D_2O	100	8·60	—	6·97	—	3·8	7·3	—	—
			$HCONH_2$	100	8·59	—	6·94	5·90	4·1	7·3	—	3·3

[a] Resonances for NH protons were observed at: *cis*, $\tau_{H_1} = 2{\cdot}45$, $\tau_{H_3} = 0{\cdot}07$; *trans*, $\tau_{H_1} = 2{\cdot}49$, $\tau_{H_3} = 0{\cdot}00$.

TABLE 2. NMR SPECTRA OF DIHYDROURACILS

Substituents			Solvent	Mc/s	Chemical shifts (τ)					Coupling constants (c/s)		
5	6	Config.			H_5	H_6	Ph	H_1	H_3	$J_{H_5H_6}$	$J_{H_5H_6}$	$J_{H_1H_6}$
H	COOH	—	D_2O	100	6·76ax 6·93eq			—	—	17·4	6·9ax 5·1eq	
			$HCONH_2$	100	7·00	5·59	—	—	—	—	—	3·0
H	COOMe	—	DMSO-d_6	100	7·08ax 7·36eq	5·76		2·22	−0·07	16·9	7·4ax 3·1eq	3·6
H	Ph	—	DMSO-d_6	60	7·13 7·37	5·28	2·65	1·98		16·5	6·8 5·8	2·6
			$HCONH_2$	60	7·17	5·20	—	—	—	—	—	~1·5
			CF_3COOH	60	6·90	5·03	2·62	—	—	—	—	—
Ph	Ph	*cis*	DMSO	60	5·85	5·00	*a*	2·00	—		5·5	1·7
			CF_3COOH	60	5·65	4·73	*a*	—	—		5·9	—
Ph	Ph	*trans*	DMSO	60	5·98	5·20	2·70	1·95	—		6·8	2·3
			DMSO + 10% CF_3COOH	60							7·5	—
			CF_3COOH	60	5·84	4·98	2·71	—	—		11·9	—

[a] Complex band.

TABLE 3. NMR SPECTRA OF 5,6-TETRAMETHYLENEDIHYDROURACIL

Config.	Solvent	Chemical shifts (τ)				Coupling constants (c/s)		
		H_X	H_Y	H_M	H_N	J_{XY}	$\lvert J_{AX} + J_{BX}\rvert$	$\lvert J_{CY} + J_{DY}\rvert$
cis	CF_3COOH	—	—	2·79	0·78	—	—	—
	CF_3COOH:D_2O 7:5	6·27	7·14	—	—	4·8	10·5	11·5
trans	CF_3COOH	—	—	2·68	0·59	—	—	—
	CF_3COOH:D_2O 7:5	6·72	—	—	—	11·1	16·1	—

TABLE 4. NMR SPECTRA OF 2-UREIDOCYCLOHEXANE CARBOXYLIC ACID[a]

Config.	Chemical shifts (τ)				Coupling constants (c/s)		
	H_X	H_Y	NH	NH_2 + COOH	J_{XY}	$\lvert J_{AX} + J_{BX}\rvert$	$\lvert J_{CY} + J_{DY}\rvert$
cis	5·96	7·39	3·76	4·26	3·0	~9·5	~11·0
trans	6·25	7·76	3·92	4·45	9·6	13·7	13·0

[a] Solutions in dimethyl sulphoxide–benzene (9:1).

TABLE 5. NMR SPECTRA AT 100 Mc/s OF α,β-DIMETHYL-β-UREIDOPROPIONIC ACIDS AND METHYL ESTERS IN D_2O

Compound		Chemical shifts (τ)					Coupling constants (c/s)		
Config.	acid/ester	Me_α	Me_β	H_α	H_β	MeO	$J_{H_\alpha Me\beta}$	$J_{H_\alpha Me\beta}$	$J_{H_\beta Me\beta}$
erythro	acid	8·85	8·84	7·40	6·08	—	6·9	7·0	6·7
threo	acid	8·86	8·86	7·36	6·09	—	7·1	6·9	6·7
erythro	ester	8·90	8·91	7·37	6·07	6·31	5·7	6·95	6·7
threo	ester	8·88	8·89	7·37	6·17	6·31	6·9	7·0	6·8

$\tau_{C_\alpha H_2}$ = 7·34 (7·42), $\tau_{C_\beta H}$ = 5·00 (5·11), τ_{NH_2} = 4·42, τ_{NH} = 3·42 (3·58), τ_{COOH} = −1·19 broad (−1·19); $J_{H_{(N)}H_\beta}$ = 8·4 (8·2), $|J_{H_\alpha H_\beta}\ \ J_{H\alpha H\beta}|$ = 14·1 (13·8).

The spectra of PhDHU were found to be strongly solvent dependant. Addition of trifluoroacetic acid to PhDHU in DMSO eliminated the H-1 to H-6 coupling, broadened the H-6 multiplet, and narrowed the two H-5 signals. In formamide the outer-line separation of the H-6 multiplet changed from 12·6 in neat DMSO to 15·0 c/s (correcting in both cases for J_{16}), and the chemical shift difference between the two protons at C-5 decreased so that the octet collapsed to a triplet with approximate intensities 2:1:1 and separations 6·3 and 2·0 c/s. In trifluoroacetic acid the C-6 proton showed as a triplet 16·0 c/s wide and C-5 proton as a doublet of a narrow and a broad line due to overlap of the intense lines of the AB quartets, and loss of the weaker lines.

Most assignments are unambiguous: the H-6 proton is coupled to H-1 and occurs at lower field than H-5 (for numbering see IV). The assignment of methyl peaks was based on the couplings with methine protons. The assignment of the individual methylene protons at position 5 is more complex. Thus, the methyl ester of DHO, according to J_{16}, has the methoxycarbonyl group predominantly axial; hence the *trans* J_{56} should be e/e and comparison suggests that J_{5e6e} is smaller than J_{5a6e} and hence the C-5 equatorial proton is at higher field which is unusual but not unknown in DHU.[4] The assignment is confirmed by long range coupling to H-1 and H-3,[4] and by the lower chemical shift of H-5 in *cis*-MeDHO as compared to the *trans* isomer, where according to coupling constant evidence, H-5 is equatorial in the former and axial in the second compound. The same choice is made less convincingly for the H-5 protons of dihydroorotic acid, while no assignment could be made for PhDHU.

Signals for N-1H and N-3H (and for NH and NH_2 in the ureido acids) and J_{16}

TABLE 6. NMR SPECTRA AT 60 Mc/s OF α,β-DIPHENYL-β-UREIDOPROPIONIC ACIDS AND METHYL ESTERS

Compound		Solvent	Chemical shifts (τ)						Coupling constants (c/s)	
Config.	acid/ester		NH	NH_2^a	H_α	H_β	MeO	Ph	$J_{H_\alpha H_\beta}$	$J_{H_\beta NH}$
erythro	acid	DMSO	3·59	4·72	6·01	4·65	—	2·6	11·5	9·8
		DMSO + 10% CF_3COOH	—	—	5·97	4·63	—		11·1	
threo	acid	DMSO-d_6[c]	3·13	4·60	6·01	5·77	—	3·75 3·80[d]	9·0	9·1
		$HCONH_2$			5·75	4·53	—		9·2	8·7
		$HCONH_2$ + 10% CF_3COOH			5·71	4·50			9·2	
erythro	ester	DMSO-d_6[c]	3·50	4·70[e]	5·88	4·62	6·65	2·6[b]	11·2	9·4
		$HCONH_2$			5·79	4·46	6·51		10·8	9·0
		$HCONH_2$ + 10% CF_3COOH			5·87	4·50	6·53		10·2	
threo.	ester	DMSO-d_6[c]	3·15	4·40	5·88	4·69	6·40	3·77 3·82[d]	9·5	9·6
		$HCONH_2$			5·78	4·56	6·31		9·8	8·6
		$HCONH_2$ + 10% CF_3COOH			5·76	4·56	6·30		9·9	

[a] In the acids the peak is common with that of COOH and integrates for 3 protons.
[b] Complex band.
[c] Dr. S. Spasov, private communication.
[d] Doublet.
[e] Broad.

were clearly observed only in DMSO. Some spectra were not scanned at sufficiently low field for the N-3H (which is down field from N-1H) or CO_2H peaks to be detected. The COOH proton signal for PhUPA in DMSO is broad (ca. 100 c/s wide, integrating for one proton), but the other ureido acids in DMSO give one signal integrating for all three CO_2H and NH_2 protons.

5,6-*Tetramethylenedihydrouracils.* These compounds (II, III) were insufficiently soluble in DMSO and were examined in trifluoroacetic acid or trifluoroacetic acid–deuterium oxide (7:5). Poor resolution of the H-6 (i.e. H_X) signal in trifluoroacetic acid improved in the aqueous mixture, probably H-1 to H-6 coupling persists in the neat acid because of slow exchange; the general band shapes were similar in both solvents, but N-1H and N-3H peaks occured for the neat acid solution only.

The spectra of the *trans* isomer (III) were best resolved in trifluoroacetic–deuterium oxide. The general methylene absorption included H_Y; the H_X multiplet approximated to the X part of a ABX system with H_X additionally coupled to H_Y to produce a double of quartets (Fig. 1A). Spin decoupling of protons A + B by irradiation within the methylene region (7·6 to 8·9 ppm) collapsed H_X to a doublet (J_{XY} = 11·0 c/s) (Fig. 1B). Irradiation of H_Y, by scanning the methylene region, changed H_X to a poorly resolved triplet (Fig. 1C) with an outer line separation of 16·0 c/s ($|J_{AX} + J_{BX}|$); however, the inner line does not compare well to the quartets of the undecoupled H_X spectrum, possibly due to incomplete decoupling. The coupling constants (J_{XY} and $|J_{AB} + J_{BX}|$) from the decoupled spectra confirm the original analysis.

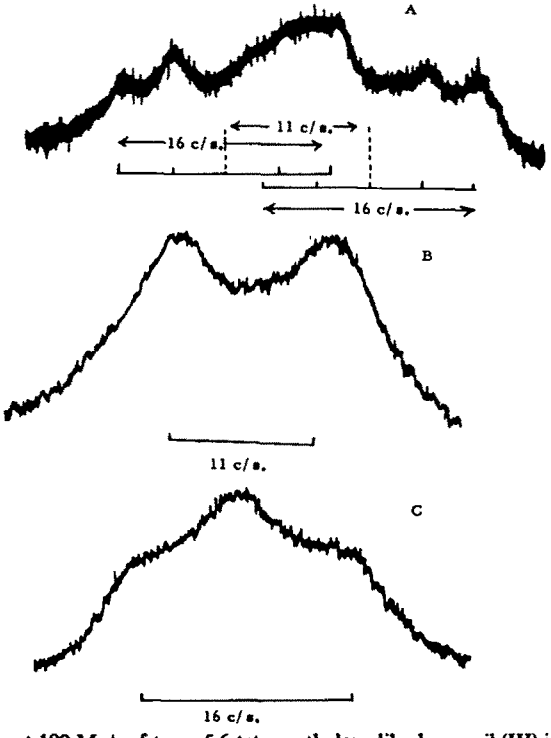


FIG. 1 NMR spectra at 100 Mc/s of *trans*-5,6-tetramethylenedihydrouracil (III) in trifluoroacetic acid-deuterium oxide: (A) H_X, undecoupled; (B) H_X with spin decoupling of H_A and H_B; (C) H_X with spin decoupling of H_Y.

The *cis* isomer (IIa ⇌ IIb) in trifluoroacetic acid showed the resolved H_X and H_Y signals as eight line multiplets, well separated from the complex cyclohexane absorption and from each other. The H_X multiplet can be interpreted as two overlapping quartets (X part of ABX with additional coupling to H_Y) (Fig. 2A).

The coupling constants measured from the undecoupled multiplet compare well with those from the doublet (J_{XY}) (Fig. 2B), and from the quartet's outer-line separation ($J_{AX} + J_{BX}$), in decoupled spectra obtained by irradiation at various positions in the cyclohexane and H_Y resonances. The ($J_{AX} + J_{BX}$) quartet is distorted by a spurious irradiation side band beating pattern. The H_Y multiplet (higher field) (Y part of CDY with additional coupling to H_X) consists of a doublet of two quartets (Fig. 2C), which are slightly asymmetric, probably due to second-order character because of the relatively small chemical shift difference between the H_Y and H_{C+D} resonance, although no additional lines could be defined. Irradiation of H_X produced a single asymmetric quartet (Fig. 2D) but irradiation of C + D was not completely achieved and gave a poorly resolved doublet (Fig. 2E) incorporating additional lines, perhaps due to an appreciable difference between the C and D chemical shifts.

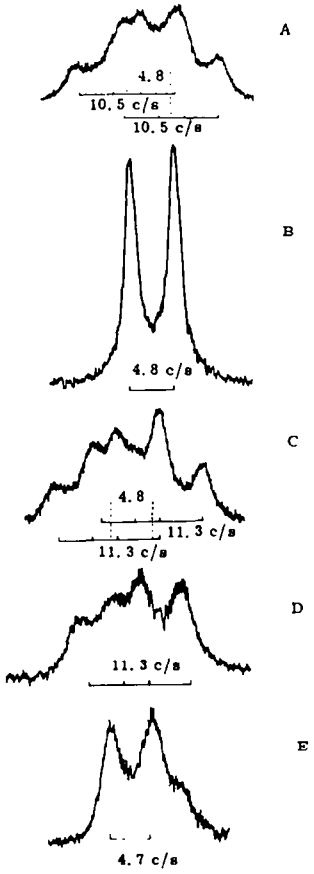
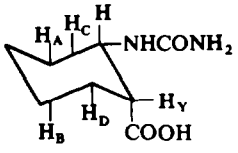
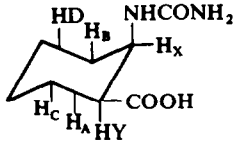


FIG. 2 NMR spectra at 100 Mc/s of *cis*-5,6-tetramethylenedihydrouracil (II) in trifuoroacetic acid: (A) H_X, undecoupled; (B) H_X with spin decoupling of H_A and H_B; (C) H_Y, undecoupled; (D) H_Y with spin decoupling of H_X; (E) H_Y with spin decoupling of H_C and H_D.

This may also affect the H_Y spectrum, but the outer line separation should still give $|J_{CY} + J_{DY}|$. The separation of the poor quality doublet (Fig. 2E) is in agreement with the other measurement of J_{XY}.



VIa



VIb

2-Ureidocyclohexanecarboxylic acids. Spectra were recorded of a 20% solution in DMSO-d_6: benzene (9:1). The coupling H_MH_X was chemically decoupled with a little of trifluoroacetic acid.

The *trans* isomer (Va ⇌ Vb), before addition of trifluoroacetic acid, disclosed a doublet (H_M, J_{MX} = 8·0 c/s) and singlet (COOH + NH_2) at low field (area ratio 1:3) with the H_X well and the H_Y just separated from the complex cyclohexane region at higher field. Spin decoupling of protons A + B in the sample without trifluoroacetic acid caused collapse of the signal for H_X into a poorly defined triplet, which on addition of trifluoroacetic acid gave a well resolved doublet (J_{XY}). Analysing the triplet as a part of AMX spectrum with one coupling constant equal to J_{XY} yields J_{MX} = 8·0 c/s. Spin decoupling of H_Y, with H_M chemically decoupled, collapsed H_X into a poorly defined quartet (Fig. 3A). The H_X signals before and after the addition of trifluoroacetic acid (Figs 3B and 3C) can be first-order analysed with J_{XY} = 9·5 c/s, $|J_{AX} + J_{BX}|$ = 13·7 c/s and J_{MX} = 8·0 c/s, as obtained from the decoupled spectra. Spin decoupling of protons C + D collapsed H_Y into a doublet. Spin decoupling of H_X gave a well resolved quartet for H_Y (Fig. 3D) in which the line separations are nearly symmetrical. The original H_Y spectrum (Fig. 3E) agrees with the calculated first-order spectrum [J_{XY} = 9·6 c/s and $|J_{CY} + J_{DY}|$ = 14·0 c/s] to within 0·2 c/s.

The *cis* isomer (VIa ⇌ VIb) gave spectra with poor resolution and coupling constants could be quoted only to ±0·5 c/s. The spectrum consists of two peaks at low field (area ratio 1:3) together with the H_X and H_Y signals and the cyclohexane absorption. The H_Y multiplet overlaps slightly with the DMSO-d_5 quintet (Fig. 4A). Undecoupled spectra of H_Y and of H_X (with trifluoroacetic acid and without) are poorly resolved, but the H_X signal narrows on addition of trifluoroacetic acid by ca. 6 c/s which coincides with the separation of the poorly defined doublet for H_M. Decoupling of protons A + B together with chemical decoupling of H_M collapses H_X into a broad doublet of separation 3 c/s (Fig. 4B). The equivalent 3 c/s doublet obtained for the H_Y resonance by irradiation of protons C + D was ill-defined due to the DMSO-d_5 quintet overlap and a spurious side band beat pattern. Spin decoupling of H_Y together with chemical decoupling of H_M, yielded a poorly resolved quartet for the H_X resonance (Fig. 4C), the outer dimensions of which indicated 9·5 c/s for $|J_{AX} + J_{BX}|$. Although the slight overlap of the DMSO-d_5 quintet interfered, the three observed lines of the similar quartet for H_Y (Fig. 4A) gave $|J_{CY} + J_{DY}|$ = 11 c/s.

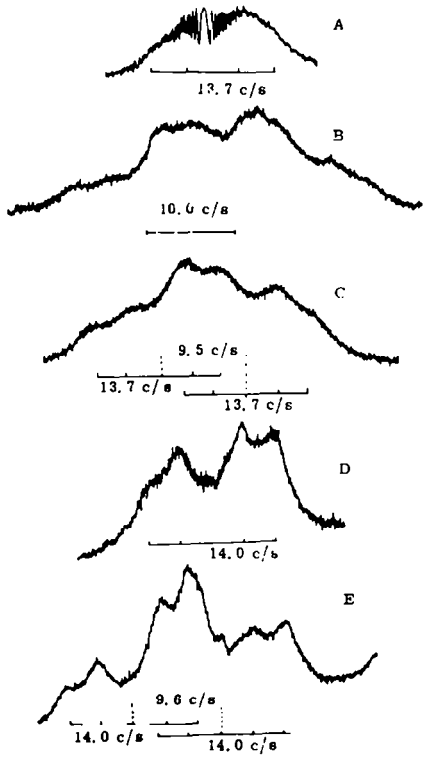


FIG. 3 NMR spectra at 100 Mc/s of *trans*-2-ureidocyclohexane carboxylic acid (V): (A) H_X with chemical decoupling of H_M and spin decoupling of H_Y; (B) H_X before addition of trifluoroacetic acid; (C) H_X after addition of trifluoroacetic acid; (D) H_Y after spin decoupling of H_X; (E) H_Y undecoupled.

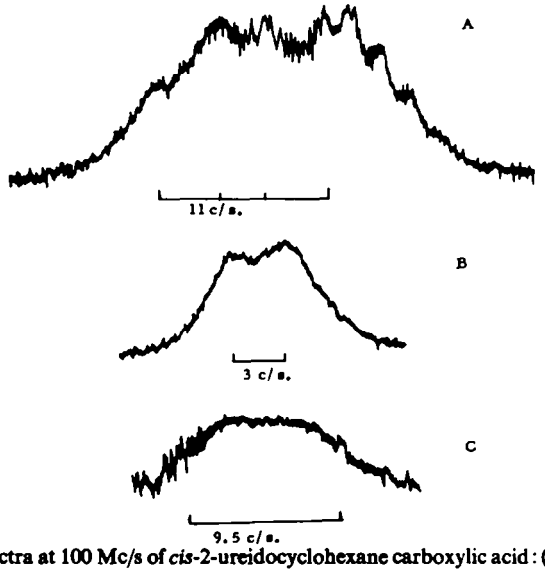


FIG. 4 NMR spectra at 100 Mc/s of *cis*-2-ureidocyclohexane carboxylic acid: (A)H_Y multiplet with spin decoupling of H_X; (B) H_X with H_M chemically decoupled and H_A and H_B spin decoupled; (C) H_X after spin decoupling of H_Y and chemical decoupling of H_M.

J_{AX}, J_{BX}, J_{CY} and J_{DY} in TMDHU and UCHA. The observed multiplets for the methine protons were treated as the X parts of ABX rather than AMX spectra because of the close proximity of resonances A and B. For the H_Y resonance in *cis*-TMDHU, the asymmetry of the quartets showed that the spectra approached an ABC case. Using the data obtained from the successive decoupling of J_{XY}, $(J_{AX} + J_{BX})$, and $(J_{CY} + J_{DY})$, and chemical shift values estimated from resonance frequencies and frequencies at which decoupling was achieved, a series of Laocoon II[18] computations was run by varying δ_{AB} (0·2 and 0·4 ppm) setting $J_{AB} = -11$ c/s. Approximate coupling constants with an estimated reliability of $\pm 0{\cdot}5$ c/s are listed below, together with the pertinent line separations observed (bracketed):

Compound		J_{AX}	J_{BX}	J_{CY}	J_{DY}
TMDHU	*trans*	4 (4·0)	12	—	—
	cis	3·5 (ca. 3·8)	7	3·5 (ca. 3·8)	8
UCHA	*trans*	3 (3·2)	10·5	3 (3·5)	11
	cis	3 (ca. 3·0)	6·5	3·5 (ca. 3·9)	7·5

DISCUSSION

Dihydrouracils. X-Ray analysis of dihydrothymine[10] has recently substantiated earlier assumptions of a half-chair conformation of dihydrouracil ring. The NH—CO—NH—CO portion of the ring is planar while the C-5 and C-6 atoms are 0·42 and 0·31 Å out of plane on opposite sides with a dihedral angle of ca. 30° between the bonds on the C-5 and C-6 atoms [the N(1)—C(6)—C(5)—C(4) dihedral angle is 27° 50′]. Roullier, *et al.*,[4] from coupling constants evidence, concluded that certain DHU derivatives with only one equatorial substituent at C-5 or C-6 are distorted planar structures with a dihedral angle around 30–50°, while other derivatives with an axial substituent possessed a dihedral angle of ca. 60°. This conclusion comes from two arguments based on the Karplus J-dihedral angle dependence: (a) larger *cis* coupling constants of 5·54 to 7·23 c/s for the "more planar" compounds in contrast to 3·3 to 4·3 c/s for the "more puckered" ones; (b) values of J_{16a} and J_{16e} of 1·5 and 3·7 c/s for the first series and 1 and 4·5 c/s for the second one.

However, there is no obvious reason for the different distortion of the dihydrouracil ring in the two series of derivatives, and the following explanations of the above observations seems more likely. For all the low *cis* couplings[4] the preferred conformation of the compound in question has a strongly electronegative axial substituent (OH or Br), which is known[19] to substantially lower *cis* couplings. Further evidence is provided by the geminal coupling constants for the methylene protons at C-5: values of 16 and 15·8 c/s, respectively, are reported[4] for 6-hydroxydihydrouracil and 6-methyldihydrouracil but the first compound is classed as more puckered and the second as more planar. Our geminal J_{5a5e} values for DHO, its methyl ester, and PhDHU (Table 2), are of the same order. Geminal coupling constants of methylene groups adjacent to carbonyl decrease (in absolute value) as the angle between the carbonyl and the methylene protons decreases, e.g. on changing from a cyclohexanone to a more planar structure.[20] The highly negative and nearly constant values for dihydrouracils suggest that all the rings are distorted from the planar configuration to approximately the same extent. The alternative explanation for the lowering of

J_{16e} and the increase in J_{16a} (see above) is that equilibria do not completely favour the preferred conformer; the H-1 proton will be in the plane of the ring (the position found by X-ray analysis[10]) in both conformations because of simultaneous inversion at the nitrogen.

The dangers of quantitative conformational analysis deductions from J values have pointed out;[21] the present paper discusses such deductions for dihydrouracil derivatives, assuming that other factors affecting the J values remain more or less constant. In addition to the J_{56} coupling constants of *trans* protons, the stereo dependence of J_{16} allows[4] estimates in derivatives for which only *cis* couplings are available.

For quantitative deductions (within the generally accepted uncertainty of such evaluations) the problem of choosing appropriate "pure" constants arises. To obtain J_{aa}, the model compound *trans*-TMDHU was studied; it is fixed in conformation III. Steric strain should tend to pucker both rings of I, hence the standard J_{aa} value obtained from J_{XY} should be larger than a normal J_{aa} in dihydrouracil and smaller than a normal cyclohexane value; further, the J_{aa} values for the couplings of the protons at C-5 and C-6 to those of the cyclohexane ring should be lower compared to the usual cyclohexane values; unexpectedly, the opposite trend is found. The observed value of $|J_{AX} + J_{BX}|(|J_{aa} + J_{ae}|)$ of 16·0 c/s and the calculated approximations for J_{AX} (J_{aa}) and J_{BX} (J_{ae}) of 12 and 4 c/s are towards the higher limits of the usual ranges for cyclohexane derivatives.[22] This is illustrated by comparison with the parent *trans*-2-ureidocyclohexane carboxylic acid (Table 4), and with related systems such as *cis*-3-methylcyclohexylamine[23] [$J_{1a2a} = 10{\cdot}6$ c/s and $J_{1a2e} = 3{\cdot}2$ c/s] or *cis*-2,6-dimethylpiperidine[24] [$J_{2a3a} = 10{\cdot}6$ c/s and $J_{2a3e} = 1{\cdot}9$ c/s (lowered by electronegativity effect)]. The J_{XY} value of 11·1 c/s is *lower* than the J_{trans} of 11·9 c/s for *trans* DPhDHU in trifluoroacetic acid. Assuming these two values to represent the usual variation in J_{aa}, the average of 11·5 c/s was taken as standard.

The spectra of the *cis* isomer of TMDHU are also significant. The *cis* coupling constants of Ref. 4, which are of reliable assignment and unaffected by electronegativity effects, and those obtained in the present study, range from 5·2 to 7·23 (average 6·2) c/s. The value of 4·8 c/s for J_{XY}, obtained from the spectrum of *cis*-TMDHU, is slightly below this range indicating some distortion of the dihydrouracil ring by the fused cyclohexane ring. The distribution between the two conformers IIa and IIb may be assessed from the observed $|J_{AX} + J_{BX}|$ and $|J_{CY} + J_{DY}|$ values as well as from the calculated individual coupling constants:

$$J_{AX} = pJ'_g + (1-p)J_g \qquad J_{CY} = J_g$$

$$J_{BX} = pJ_g + (1-p)J_t \qquad J_{DY} = pJ_t + (1-p)J_g$$

Here p is the fraction with NH axial and J'_g is a *gauche* constant reduced by a directed electronegativity effect. In cyclohexylamine systems 2·5 c/s compared to the normal value of 3·0 c/s is quoted.[19] If p is around 0·5 then $|J_{AX} + J_{BX}|$ should be slightly lower than $|J_{CY} + J_{DY}|$, which is observed in the trifluoroacetic acid/deuterium oxide mixture. The electronegativity effect is not shown by the calculated J_{AX} and J_{CY} values which are equal, these are however uncertain to 0·5 c/s. On the other hand J_{BX} is 1 c/s less than J_{DY} indicating a p value of slightly greater than 0·5. Thus

in this solvent both conformers of *cis*-TMDHU are either equally populated or there is a slight predominance of conformer IIb.

The only experimental J_{ee} values for DHU reported[4] are for certain hydroxy and bromo derivatives. These fall into two ranges, from 1·7 to 2·2 and from 3·0 to 3·4 c/s. No corellation between the J values and electronegativities is observed, and the higher values are therefore attributed to some participation of diaxial coupling. The average for the lower range, i.e. 2·0 c/s, was taken as J_{ee}. These values were obtained from monohydroxy or monobromo derivatives so that an electronegativity correction of ca. 10% would hardly effect the results. For the standard J_{16a} and J_{16e}, 1 and 4·5 c/s were adopted following ref. 4; these values are averages of the coupling constants for the "more planar" compounds.

TABLE 7. CONFORMATION OF DIHYDROURACIL DERIVATIVES

Compound	Solvent	% Equatorial substituent[a] from J_{trans}	from J_{16}
5-Hydroxy-DHU[b]	DMSO-d_6	87	80
5-Bromo-DHU[b]	DMSO-d_6	15	9
6-Methyl-DHU[b]	DMSO-d_6	79	—
5-Methyl-DHU[b]	DMSO-d_6	82	78
trans-DMeDHU	DMSO-d_6	79	86[c]
	$HCONH_2$	85	—
cis-DMeDHU	DMSO-d_6	—	40
	$HCONH_2$	—	46
DHO	D_2O	33	—
	$HCONH_2$	—	43
DHO Me ester	DMSO-d_6	15	26
cis-MeDHO	$HCONH_2$	—	37
trans-MeDHO	$HCONH_2$	22	34
	1:1 $HCONH_2$:D_2O	19	—
PhDHU	DMSO-d_6	41(50)[d]; 46[e]	54
	$HCONH_2$	72[e]	86[c]
	CF_3COOH	82[e]	—
cis-DPhDHU	DMSO	—	20
trans-DPhDHU	DMSO	50	54
	DMSO + 10% CF_3COOH	58	—
	CF_3COOH	~100	—

[a] That at C-6 is given when two.
[b] Based on J values from Ref. 4.
[c] Approximate due to uncertainty in J_{16}.
[d] Two values are given since J_{trans} could not be assigned.
[e] From band width of H-6 resonance.

Table 7 lists the percentages of conformer population based on the above standard J values. No errors were estimated since the results are only semiquantitative. Several examples from Ref. 4 are included. The populations obtained by the two modes of of calculation, where both are available, agree within 15%, which supports our contention that the lower J_{16e} values reported in Ref. 4 are indeed due to variations in conformational equilibria rather than in degree of ring distortion.

It is not obvious whether substituents in DHU should be expected to prefer equatorial or axial positions. The axial orientation for substituted cyclohexanes is destabilised by *cis*-1,3-diaxial interactions with hydrogen atoms: however in DHU these hydrogen atoms are replaced by a π-electron system on sp^2-hydrised NCNC-framework. Indeed, for similar systems it is becoming increasingly clear that (pseudo) *axial* positions are preferred for bulky substituents as occurs for 9,10-dihydrophenanthrenes,[25] 1,2-dihydronaphthalenes,[26] and 1,4-benzodioxanes.[27]

The data obtained from *trans*-DMeDHU confirm the finding[4] that methyl groups prefer the equatorial positions. The two conformers of *cis*-DMeDHU are equally populated in DMSO and formamide. If, as in the case of *cis*-TMDHU, this distribution is taken as a measure of the interaction [Me:CO] versus [Me:NH] the situation with *cis*-DMeDHU is similar to that of *cis*-TMDHU is trifluoroacetic acid/deuterium oxide.

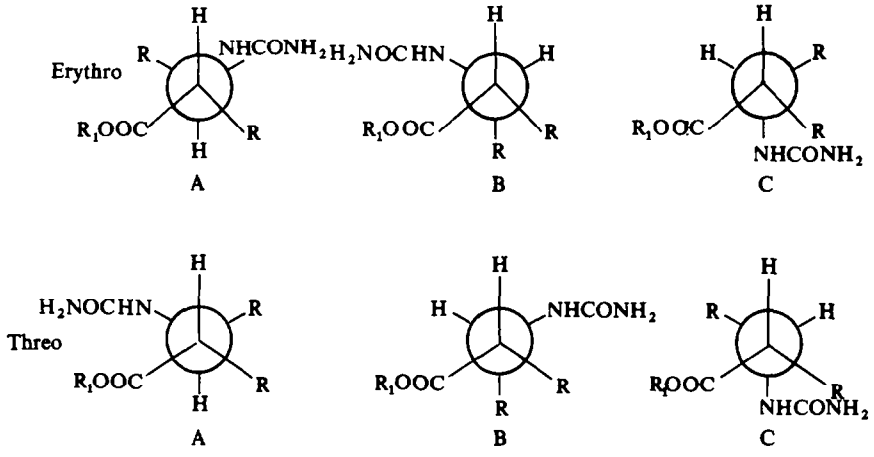
The carboxyl group prefers the axial position in DHO and in *trans*-MeDHO. This orientation is not due to hydrogen bonding involving the carboxyl group as demonstrated by the even stronger preference for the axial position of the methoxycarbonyl group in the methyl ester of DHO. Dipole interactions favour the axial position for these groups, but the observation that a single Ph at C-6 in PhDHU is evenly distributed between the axial and equatorial positions suggests the importance of other factors. In DMSO, the ee and aa forms of *trans*-DPhDHU are equally populated, in contrast to the ee predominance for *trans*-DMeDHU.

The relative "sizes" of these groups are $CO_2Me < Me < Ph$, as measured by their axial-equatorial equilibrium in cyclohexane, so *simple* explanations of the above phenomena based on relative size are ruled out. However, it is becoming apparent that the *shapes* as well as the gross sizes of substituent groups are important in determining conformational equilibria: thus, the preference for the equatorial position of the mono-substituted cyclohexane *decreases* in the series NH_2, NHMe, NMe_2.[28] This behaviour of the aminocyclohexanes can be rationalised in terms of specific intramolecular interactions of the individual conformers.[28] We believe a similar explanation applies to the dihydrouracils, but at present we have insufficient data to discuss this in terms of specific interactions.

The strong solvent dependence of the conformational equilibria in PhDHU and *trans*-DPhDHU are of interest. In formamide and trifluoroacetic acid, no individual values for the vicinal couplings could be obtained for PhDHU. The analysis was therefore based on the outer line separations of the H-6 resonance: $|J_{AX} + J_{BX}| = p|J_{aa} + J_{6a5e}| + (1 - p)|J_{6e5a} + J_{ee}|$; where $J_{aa} = 11{\cdot}5$ c/s, $J_{6e5a} = J_{6a5e} = 6{\cdot}2$ c/s, and $J_{ee} = 2{\cdot}0$ c/s. J_{6a5e} is probably lower than J_{6e5a} due to the stereospecific electronegativity effect of the ring nitrogen; in 5-methyldihydrouracil a value as low as 4·06 for J_{6a5e} was reported,[4] so that the values quoted in Table 7 for the percentage of Ph equatorial are probably low, but other uncertainties do not warrant any refinement. Irrespective of the exact values, changing the solvent from dimethylsulphoxide to formamide to trifluoroacetic acid successively shifts the equilibrium in favour of the conformer with equatorial phenyl.

The same phenomenon was observed in the case of *trans*-DPhDHU where the proportion of the diequatorial conformer shifts from 50% in DMSO to approaching 100% in trifluoroacetic acid. These equilibrium changes cannot be attributed to protonation in trifluoroacetic acid, since the pK_{BH3+} of dihydrouracils are more

negative than the H_0 of CF_3COOH (pK_{BH+} of dihydrouracil itself has been estimated as ca. −4·5). Solvation apparently significantly changes the interaction of the axial phenyl, or other substituent, with the dihydrouracil ring; possibly the geometry of the ring is also affected slightly. More detailed discussion necessitates further investigation.



SCHEME 1

β-*Ureido acids*. Conformers A, B and C (see Scheme 1) exist for the diastereoisomeric pairs of 2-methyl-3-ureidobutyric acids (MeUBA), 2,3-diphenyl-3-ureidopropionic acids (DPhUBA), and their methyl esters as a result of rotation round the αC–βC bond. An approximate evaluation of the distribution between conformers A and B + C can be made from the $J_{\alpha\beta}$ values, provided the appropriate J_t and J_g values are known. The J_g value in conformation C should be lower than that in B, although as nitrogen is only 0·5 units more electronegative than carbon, the difference is small. Some such estimates of conformer populations[30] are consistent with the more rigorous variable temperature method, but with others, such as phenylalanine,[31] the variable temperature results could be rationalised only be assuming considerable deviation from classical behaviour; i.e. dihedral angles deviating from 60° or temperature variables energy differences between the conformers. Hence the conformer distributions we now derive are less certain than those obtained above for the cyclic systems.

cis-2-Ureidocyclohexane carboxylic acid (UCHA) exists in two conformers (VIa and VI), equivalent to the erythro rotamers B and C; hence $J_g \simeq J_{XY} = 3{\cdot}0$ c/s. The sums $|J_{AX} + J_{BX}|$ and $|J_{CY} + J_{DY}|$ reflect the conformational equilibrium of *cis* UCHA. As with *cis*-TMDHU $|J_{AX} + J_{BX}|$ is smaller, the difference in the present series is 1·4 c/s, indicating that the ureido group is predominantly axial and the carboxyl group predominantly equatorial (in DMSO).

If in *trans*-UCHA, the substituents were wholly diequatorial (conformer Va), then $J_t = J_{XY} = 9{\cdot}6$ c/s. This value of J_t is obviously too low as $J_{H\alpha H\beta}$ values of up to 11·5 c/s are observed (Table 6). For amino acids, with similar substituents a J_t value

of 13·56 c/s has been recommended.[33] However, the value of 11·5 c/s adopted for the DHU derivatives where the dihedral angle is close to 150° gives, from a Karplus type of dependence, $J = A\cos^2\psi$, for a dihedral angle of 180°, $J_t = 15{\cdot}3$ c/s. The intermediate value for J_{aa} of 13·0 c/s gives the populations of Table 8 which have only semiquantitative significance.

TABLE 8. CONFORMATION OF ACYCLIC DERIVATIVES

Compound	Solvent	%A
erythro-MeUBA	D_2O	39
threo-MeUBA	D_2O	41
erythro-MeUBE[a]	D_2O	27
threo-MeUBE[a]	D_2O	39
erythro-DPhUPA	DMSO	85
	DMSO + 10% CF_3COOH	81
threo-DPhUPA	DMSO-d_6	60
	$HCONH_2$	62
erythro-DPhUPE[b]	DMSO-d_6	82
	$HCONH_2$	78
	$HCONH_2$ + 10% CF_3COOH	72
threo-DPhUPE[b]	DMSO-d_6	65
	$HCONH_2$	68

[a] MeUBE stands for 2-methyl-3-ureidobutyric acid methyl ester.
[b] DPhUPE stands for 2,3-diphenyl-3-ureidopropionic acid methyl ester.

On the adopted scale of $J_g = 3{\cdot}0$ c/s and $J_t = 13{\cdot}0$ c/s in *trans*-UCHA the substituents are only 65% diequatorial which seems unreasonably low. For *erythro*-MeUBA and the corresponding ester MeUBE, the low fraction of conformer A suggests attraction between the ureido and carboxyl groups, other than H-bonding of the carboxyl to the ureido group (the latter as proton acceptor), favouring conformers B + C. Bothner-By has suggested attraction between freely rotating dipoles as the explanation for a similar observation in meso 2,3-diacetoxybutane.[32] The distribution observed with the *threo* isomers of MeUBA and its ester neither contradicts nor requires such an assumption.

Conformer A is preferred for the threo isomers of DPhUPA. Recent reports,[33–37] show that *gauche* Ph groups in threo 1,2-diphenylethane derivatives are frequently met; synclinal Ph groups are oriented "face to face" and π-interaction may reduce the repulsion between the two groups. Such an assumption is supported by LCAO-MO calculation of the interaction between the two phenyls in 1,2-diphenylethane in synperiplanar conformation where an attraction of ca. 0·5 kcal/mole was found.[38] Thus the three steric interactions between the substituents in conformers B and C appear to be more severe than the two in conformer A.

The two types of attraction postulated, those between the ureido and the carboxyl group, and between the two phenyls are apparently small as evidenced by the preference of conformer A in *erythro*-DPhUPA and its ester. Conformers B + C are strongly preferred for *erythro* derivatives where strong attraction is present as in *erythro* 2-amino-1,2-diphenylethanol[34] and its N,N-dimethyl derivative.[37]

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