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Commentationes

Spectra-Structure Relationships in the Near Ultraviolet Optical Activity of Chiral Barbituric Acid Derivatives

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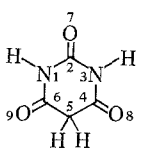
The chiroptical properties associated with the n-π^* (singlet-singlet) transitions in dissymmetric barbituric acid derivatives are examined on the basis of two theoretical models. The lower singlet excited states of unsubstituted and alkyl substituted barbituric acids are calculated on the semi-empirical CNDO/S-CI molecular orbital model, and the spectroscopic properties associated with transitions to these states are computed. In the structures we examined, three n-π^* transitions are found at $\lambda > 220$ nm, two of which are nearly degenerate. Each of these transitions is computed to be strongly magnetic dipole allowed and to be forbidden or very weak (depending upon the exact symmetry and geometry of the trioxopyrimidine moiety) in electric dipole radiation. Contributions from chiral distortions within the trioxopyrimidine chromophoric system to the rotatory strengths of the three lowest energy n-π^* transitions are calculated directly from wave functions obtained by the CNDO/S-CI method. Contributions to the n-π^* rotatory strengths arising from "vicinal" interactions between the trioxopyrimidine chromophore and asymmetric substituent groups are calculated by a perturbation method based on an independent systems representation of the optically active compounds. Various spectra-structure relationships are considered and correlations between experimental data and theoretically calculated results are examined.

Key words: Barbituric acid, dissymmetric derivatives of ~

1. Introduction

Relationships between chemical structure, physical properties, and pharmacological activity of barbituric acid derivatives (barbiturates) have been widely studied. The 5,5-dialkylbarbituric acids are highly active molecules in biological systems and their pharmacological importance has been recognized and exploited



(I)

for many years. Despite the extensive use of these compounds in medical and biological studies, the molecular basis of their mode of action is still not clearly understood. The best known pharmacological activity of barbiturates is their sedative (hypnotic) action on the central nervous system. The parent compound,

unsubstituted barbituric acid (I), does not exhibit hypnotic activity. Such activity appears only when the C(5) ring atom is disubstituted with nonpolar groups such as ethyl, hexyl, isoamyl, phenyl, etc. It is generally believed that the presence of hydrophobic, lipophylic side chains at C(5) are necessary because of the probable action of these molecules (as hypnotic agents) in nonpolar regions, possibly at membranes. The stereochemical and electronic structural features of both the trioxopyrimidine moiety and the C(5) substituents are of potential importance for elucidating the mechanism of pharmacological action of the barbiturate systems.

Crystallographic studies [1] on a number of 5,5-dialkylbarbituric acids reveal that, in the solid state, the molecules are in the triketo tautomeric form and the trioxopyrimidine ring system may be either planar or slightly puckered. The presence and degree of puckering appear not to depend in any obvious way upon the nature of the alkyl substituents and may be due solely to crystal forces. However, the asymmetries of ring puckering observed in the various 5,5-dialkyl barbiturate crystals studied are strikingly similar, although the molecular environments in these crystals are in some cases quite different. The crystallographic results also show that the alkyl substituents assume an extended conformation with the C–C backbone disposed perpendicular to the ring in a plane which includes the C(5) and C(2) ring atoms. That is, the hydrocarbon chains of the alkyl substituents are directed perpendicular to the barbituric acid ring.

Molecular orbital studies based on the semiempirical PCILO (Perturbative Configuration Interaction using Localized Orbitals) method have been carried out by Pullman, Coubeils, and Courriere [2] for a number of 5,5-disubstituted barbituric acid derivatives. In these studies the trioxopyrimidine system was assumed planar and the total energy and net atomic charges were calculated as functions of conformational variables characteristic of C(5) substituent stereochemistry. These calculations reveal that neither the chemical nature nor the conformational aspects of the substituents attached to C(5) exert a significant perturbation on the ground state electronic charge distributions in the barbituric ring. Furthermore, the conformational energy maps reported by Pullman *et al.* [2] indicate the preference for specific conformations (within the substituent groups) which "correspond to a tendency for at least a partial folding of the aliphatic substituents towards the barbituric ring, and the eclipsing by the cyclic substituents (phenyl and cyclohexyl) of the bonds ending at C(5)". These latter, theoretically calculated, results agree with available experimental data obtained from X-ray crystallography [1].

Recently, Carroll and Sobti [3] have reported a very thorough experimental study of the near ultraviolet chiroptical properties of (*S*)-5-alkyl-5-(2′-pentyl) barbituric acids in a number of solvents. Chiroptical properties are exceedingly sensitive probes of molecular stereochemistry and electronic structure and can provide considerable structural information about species in solution. However, prerequisites to the full exploitation of these properties as structure probes are: (1) a reasonably accurate description of the electronic transitions responsible for the chiroptical observables; and, (2) a model upon which spectra-structure relationships can be based. Generally, both empirical data and theoretical calculations (or formalism) are required to construct spectra-structure relationships which are useful and which have reliable predictive value. The primary purpose of the

present study is to examine the empirical results of Carroll and Sobti [3] on a theoretical model which relates specific molecular electronic and stereochemical properties of dissymmetric barbituric acid derivatives to the chiroptical observables.

Carroll and Sobti reported the appearance of three Cotton effects (CE) in the 200–300 nm region of the circular dichroism (CD) spectra obtained on a series of (*S*)-5-alkyl-5-(2′-pentyl) barbituric acids. These CE's are centered around 260, 240, and 212 nm, and solvent studies indicate that the 260 nm and 212 nm CE's arise from n-π^* and π-π^* transitions, respectively. Carroll and Sobti further suggested that the intermediate CE (near 240 nm) may be due either to an n-σ^* transition or to a second n-π^* transition. The experimental CD spectra in the 230-270 nm region does not exhibit two clearly resolved bands; rather, the CD in this region is all of the same sign and the existence of two separate CE's must be deduced from the appearance of shoulders or a double-humped CD band. The CD band centered at 212 nm is of opposite sign to that (or those) observed in the 230–270 nm region.

The CD bands at $\lambda > 230$ nm were observed to undergo red shifts on changing from polar to less polar solvents and the observed absorption intensities in this region were reported to be weak. On the other hand, the CD band centered around 212 nm was blue shifted on going from polar to less polar solvents and the absorption intensity in this region was observed to be moderately high ($\varepsilon \sim 7400$). These observations strongly suggest that n-π^* transitions are implicated in the spectral properties observed in the 230–270 nm region and that the 212 nm CE can, indeed, be assigned to a π-π^* transition.

The sign patterns and intensities observed in the CD spectra of a 1,3-dimethyl derivative ((*S*)-5-ethyl-1,3-dimethyl-5-(2′-pentyl) barbituric acid) in various solvents are very similar to those observed for the 1,3-dihydro derivatives, suggesting that neither enolization nor association are important factors in determining the CD properties of the chiral barbituric acids studied by Carroll and Sobti [3]. pH- and concentration-dependence studies also support this conclusion.

One may expect that *three* n-π^* transitions derived from the three carbonyl moieties of the trioxopyrimidine system will possibly contribute to the near ultraviolet spectroscopic properties of barbituric acids. It can be further anticipated that two of these transitions will be nearly degenerate reflecting the presumably near-equivalence of two of the carbonyl groups. This heuristic view of the system would lead, then, to the prediction that two n-π^* CE's should be observable in the near ultraviolet CD spectrum, one arising from a single nondegenerate n-π^* transition and one arising from a nearly degenerate pair of n-π^* transitions. One may further expect the *pi* orbitals of the trioxopyrimidine system to be significantly delocalized about the ring and the carbonyl oxygen atoms. This extension of the *pi* system about the ring would make the detailed nature of the $n\pi^*$ states quite sensitive to deviations of ring conformation from planarity. Conformational alterations in the ring will, then, be reflected in the chiroptical properties of the n-π^* transitions. The study presented here was devoted to calculating the lower electronic excited states (singlets) of the trioxopyrimidine system (substituted and unsubstituted) for several ring geometries, calculating the chiroptical properties associated with transitions to these states in a number of optically active barbituric

acid derivatives, and constructing spectra-structure relationships applicable to the chiroptical spectra of these systems.

The crystallographic results on 5-substituted barbituric acid derivatives [1] suggest that the trioxopyrimidine moiety is neither rigidly planar nor rigidly non-planar. It is likely that for barbituric acid systems in solution the conformation of this moiety will be determined in large part by the detailed nature of the substituent groups and by solute-solvent interactions. The near ultraviolet optical activity of barbituric acids containing chiral substituent groups can arise from: (1) "vicinal" interactions between a symmetric trioxopyrimidine chromophore and the chiral centers of the substituent groups(s); (2) a dissymmetrically distorted (inherently chiral) trioxopyrimidine chromophore; (3) both dissymmetric vicinal interactions and inherent chirality within the chromophoric unit.

We employed two different methods in calculating the chiroptical properties associated with the three lowest lying n-π^* (singlet-singlet) transitions in dissymmetric barbituric acid derivatives. To evaluate the n-π^* rotatory strengths originating with chiral distortions of the trioxopyrimidine system we calculated the electronic wave functions of the distorted structures using the CNDO/S-CI molecular orbital model of Jaffé and coworkers, [4, 5] and then employed these wave functions in calculating directly the rotatory strengths of transitions to the three lowest lying singlet electronic states. To calculate the n-π^* rotatory strengths for structures in which the trioxopyrimidine chromophore is planar and symmetric (achiral), we adopted an independent systems model in which interactions between chiral substituents (attached at the C(5) position) and the trioxopyrimidine chromophore are treated by perturbation methods.

2. Direct Calculations of Spectroscopic Properties

2.1. Method

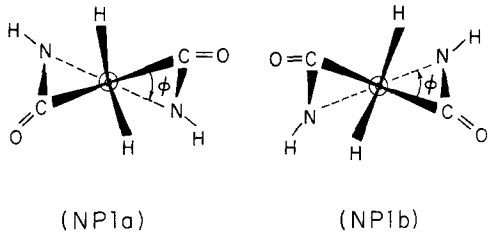
We employed the CNDO/S-CI molecular orbital model developed by Jaffé and coworkers [4, 5] to calculate wave functions for the ground and lower excited states of the systems of interest. Only singly excited configurations were included in our construction of the excited state wave functions. The wave functions calculated with the CNDO/S-CI procedure were then used to calculate the electric and magnetic dipole transition moments of transitions between the ground and lower excited states. These transition moments were subsequently used to compute the rotatory strengths (1) of the respective transitions.

$$R_{i\to j}=\mathrm{Im}\langle\psi_i|\hat{\boldsymbol{\mu}}|\psi_j\rangle\cdot\langle\psi_j|\hat{\boldsymbol{m}}|\psi_i\rangle \tag{1}$$

where $\hat{\boldsymbol{\mu}}$ is the electric dipole moment operator and $\hat{\boldsymbol{m}}$ is the magnetic dipole moment operator. The electric dipole transition moments were calculated in the dipole velocity formalism and all one- and two-center contributions to the electric and magnetic dipole transition integrals were included in the calculations. [6]

2.2. Structures

CNDO/S-CI calculations were carried out on ten structures: (a) three conformational isomers of unsubstituted barbituric acid, one with a planar ring and two



(NP1a) (NP1b)

Fig. 1. Enantiomeric forms of the skewed (or twist) boat structure of unsubstituted barbituric acid. NP1 conformation

with nonplanar rings; (b) three conformational isomers of 5-methylbarbituric acid, one with a planar ring and two with nonplanar rings; (c) one conformational isomer of 5-fluorobarbituric acid (nonplanar ring); (d) two conformational isomers of 5,5-dimethylbarbituric acid, one with a planar ring and one with a nonplanar ring; and, (e) one conformational isomer of 1,3-dimethylbarbituric acid (planar ring). In four of these ten structures the trioxopyrimidine system was planar. Atomic coordinates for the planar trioxopyrimidine system were obtained from X-ray crystallographic data (adjusted to give a structure with exact C_{2v} symmetry) on barbital [1a]. The trioxopyrimidine system in six of the ten structures was nonplanar.

Two different nonplanar conformations of the trioxopyrimidine system were considered in this study. In the one conformation (referred to as NP1 in Table 2) this moiety has a skewed (or twist) boat structure as depicted in Fig. 1. The twist angle (ϕ in Fig. 1) was given a value of 6° and bond distances in this structure were maintained at the same values as occurred in the planar structure. The trioxopyrimidine system has exact C_2 symmetry in the NP1 conformation with the C_2 axis passing through ring atoms C(2) and C(5). The two enantiomeric forms of unsubstituted barbituric acid in the NP1 conformation are shown in Fig. 1. The second nonplanar conformation of the trioxopyrimidine moiety (referred to as NP2 in Table 2) was that found most commonly in crystal structures of barbituric acid derivatives. In this conformation the trioxopyrimidine ring is slightly folded along the line C(4)–N(1). Atoms N(1), C(2), N(3), and C(4) are coplanar and atoms C(4), C(5), C(6) and N(1) are also nearly coplanar. We chose a value of 4.5° for the dihedral angle between these two planes of the halves of the pyrimidine ring and adopted the coordinates for this structure (NP2) from available crystallographic data [1]. The trioxopyrimidine system is entirely asymmetric in the conformational form NP2.

2.3. Results

The spectroscopic properties computed for the three lowest energy singlet-singlet transitions in the four structures with planar trioxopyrimidine moieties are listed in Table 1. Three of these structures have exact C_{2v} symmetry and one has exact C_s symmetry. The first two transitions in each of these structures involve excitations from "in-plane" $2p$ orbitals on oxygen atoms O(8) and O(9) to "out-of-plane" $2p$ orbitals on atoms C(2), O(7), C(4), O(8), C(6), and O(9). These transitions can best be characterized as n-π^* transitions originating with "n"

Table 1. Computed properties for compounds with planar trioxopyrimidine moiety

Compound[a]	Dipole Moment[b]	Transition	ΔE(eV)	λ(nm)	f	Symmetry
1,3-dimethyl BA	0.20	1	4.25	292	0.0016	B_2
(C_{2v})		2	4.27	291	0	A_2
		3	5.06	245	0	A_2
BA	0.85	1	4.35	285	0.0023	B_2
(C_{2v})		2	4.38	283	0	A_2
		3	5.08	244	0	A_2
5-methyl BA	1.80	1	4.38	283	0.0011	A''
(C_s)		2	4.42	281	0.0014	A'
		3	5.12	242	0	A'
5,5-dimethyl BA	1.95	1	4.37	284	0.0046	B_2
(C_{2v})		2	4.39	282	0	A_2
		3	5.22	238	0	A_2

[a] BA denotes unsubstituted barbituric acid (I).
[b] expressed in Debye units.

orbitals localized on O(8) and O(9) and terminating in carbonyl group π^* orbitals involving all three carbonyl moieties in the system. The third transition in each structure originates with an "n" orbital on O(7) and terminates in carbonyl group π^* orbitals involving all three carbonyl groups. The three lowest excited states, then can be characterized as $n\pi^*$. The transition densities of the first two transitions have some localized character (on the C(6)–O(9) and C(4)–O(8) groups) as well as some charge-transfer character (from O(9) and O(8) to C(2)–O(7)). The transition density of the third transition is partially localized on the C(2)–O(7) group and it also reflects some charge-transfer from O(7) to the C(6)–O(9) and C(4)–O(8) groups. Each of the transitions is magnetic dipole allowed by symmetry and the computed values for the magnetic dipole transition moments are indeed quite large (Table 2). Only the first transition in the structures with C_{2v} point group symmetry is electric dipole allowed, and the oscillator strengths computed for this transition are small (Table 1).

Table 2. Magnetic dipole transition moments computed for the three lowest singlet-singlet transitions in unsubstituted and 5,5-dimethyl substituted barbituric acid (planar conformation)

Compound[a]	Transition	$\lvert\langle\hat{m}\rangle\rvert$ (in Bohr magnetons)
BA	1 (B_2)	1.535
	2 (A_2)	0.837
	3 (A_2)	0.908
5,5-dimethyl BA	1 (B_2)	1.462
	2 (A_2)	0.881
	3 (A_2)	0.902

[a] BA denotes unsubstituted barbituric acid.

Table 3. Electron density differences between ground and lower excited (singlet) states

Compound[a]	Transition	Atom[b] 1	2	3	4	5	6	7	8	9
BA	1	−0.027	0.110	−0.027	0.219	−0.100	0.219	0.005	−0.198	−0.198
(planar)	2	−0.027	0.177	−0.027	0.182	−0.102	0.182	0.030	−0.205	−0.205
	3	−0.054	0.286	−0.054	0.129	−0.042	0.129	−0.369	−0.013	−0.013
5,5-dimethyl BA	1	−0.008	0.115	−0.008	0.210	−0.113	0.210	0.032	−0.131	−0.131
(planar)	2	−0.009	0.166	−0.009	0.187	−0.107	0.187	0.045	−0.133	−0.133
	3	−0.034	0.265	−0.034	0.104	−0.032	0.104	−0.354	−0.010	−0.010
1,3-dimethyl BA	1	−0.021	0.113	−0.021	0.225	−0.101	0.225	0.021	−0.198	−0.198
(planar)	2	−0.024	0.176	−0.024	0.195	−0.195	0.195	0.033	−0.208	−0.208
	3	−0.066	0.280	−0.066	0.137	−0.034	0.137	−0.367	0.006	0.006

[a] BA denotes unsubstituted barbituric acid.

[b] Atomic numbering system is as follows:

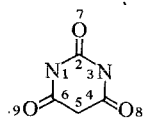


Table 4. Computed properties for compounds with nonplanar trioxopyrimidine moiety

Compound[a, b]	Dipole Moment[c]	Transition	ΔE(eV)	λ(nm)	f	R^d	Symmetry
BA (NP1a)	0.90	1	4.35	285	0.0020	− 7.02	B
(C_2)		2	4.38	283	0.0001	5.70	A
		3	5.06	245	0.0001	− 3.26	A
5-methyl BA (NP1a)	1.17	1	4.39	282	0.0030	5.27	—
(C_1)		2	4.49	276	0.0010	− 3.72	—
		3	5.08	244	0.0001	1.93	—
5-fluoro BA (NP1a)	1.16	1	4.33	286	0.0004	− 5.38	—
(C_1)		2	4.37	284	0.0015	6.34	—
		3	5.09	244	0	− 0.08	—
5,5-dimethyl BA (NP1a)	1.36	1	4.40	282	0.0020	−11.73	B
(C_2)		2	4.55	272	0.0004	5.70	A
		3	5.09	243	0	− 2.11	A
BA (NP2)	1.10	1	4.37	284	0.0019	− 3.29	—
(C_1)		2	4.41	281	0.0001	2.61	—
		3	4.92	252	0	− 0.58	—
5-methyl BA (NP2)	1.45	1	4.35	285	0.0007	− 4.04	—
(C_1)		2	4.44	279	0.0014	2.40	—
		3	4.89	253	0.0001	1.19	—

[a] BA denotes unsubstituted barbituric acid (I).
[b] NP1 = idealized nonplanar structure; NP2 = nonplanar structure derived from crystallographic results.
[c] expressed in Debye units.
[d] expressed in 10^{-40} cgs units.

Changes in electron density at various atomic sites in the trioxopyrimidine system which occur upon excitation from the ground state to the three lowest singlet excited states are listed in Table 3.

The properties calculated for the structures with nonplanar trioxopyrimidine moieties are displayed in Table 4. As was the case for the planar systems the three lowest singlet states are $n\pi^*$, the first two being somewhat localized on the C(4)–O(8) and C(6)–O(9) groups and the third being somewhat localized on the C(2)–O(7) group.

3. Perturbation Calculations of n-π^* Rotatory Strengths

3.1. Method

An independent systems model was used in calculating the n-π^* rotatory strengths of structures in which the trioxopyrimidine chromophore is planar and symmetric but on which asymmetric substituents are attached at the C(5) position. The independent systems model as employed in calculations of molecular optical activity has been described by a number of authors [7] and will not be discussed in detail here.

In the study reported here, we were interested in calculating the rotatory strengths of the three lowest energy n-π^* transitions localized on the trioxopyrimidine chromophore. Based on the molecular orbital calculations reported in Section 2 each of these transitions can be characterized as strongly magnetic dipole allowed and, in the case of an unsubstituted or symmetrically disubstituted trioxopyrimidine system, only one of these transitions has a nonvanishing electric dipole transition moment (and it is small). The molecular orbital calculations on the planar trioxopyrimidine systems also show that the three lowest n-π^* transitions break out into a nearly degenerate pair at longer wavelengths ($\sim$280–290 nm) and a shorter wavelength transition near 245 nm. The two lower energy transitions involve excitations somewhat localized on the two carbonyl moieties, C(4)–O(8) and C(6)–O(9), while the higher energy transition involves an excitation principally localized on the C(2)–O(7) group. In our perturbation calculations we represented the trioxopyrimidine chromophore by three "independent" carbonyl groups, two of which are identical (C(4)–O(8) and C(6)–O(9)) and one of which is unique (C(2)–O(7)). This representation is crude, but it is likely to be satisfactory for the treatment of the n-π^* spectroscopic properties of the system.

The asymmetric substituents attached to the pyrimidine ring at C(5) were treated as perturber groups in our independent systems model. The n-π^* transitions of the trioxopyrimidine chromophore gain their optical activity through coupling with, or interactions with, these asymmetric substituent groups. In this study we considered only uncharged and relatively nonpolar substituent groups. We assumed a dynamic coupling mechanism for the interactions between the asymmetric substituent groups and the $n\pi^*$ states of the chromophore. The n-π^* transitions are both magnetic dipole and electric quadrupole allowed, and the lowest order (and largest) term in the multipolar expansion of the chromophore-perturber interaction potential is the dipole (perturber)-quadrupole (chromophore) term. Assuming isotropic perturber groups, the dynamical coupling contri-

butions to the rotatory strength of the magnetic-dipole allowed n-π^* transitions are given by [7a]:

$$R_n = -15 \sum_i M_n^{\alpha} Q_n^{\beta\gamma} |\varepsilon_{\alpha\beta\gamma}| \sum_j \bar{\alpha}_j(\nu_n) X_j Y_j Z_j R_j^{-7} \tag{2}$$

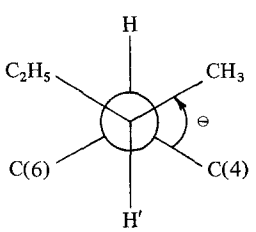
where (X_j, Y_j, Z_j) are the Cartesian positional coordinates of perturber group j referred to an origin located in the chromophore group, R_j is the radial distance between perturber j and the chromophoric group, $\bar{\alpha}_j(\nu_n)$ is the mean, isotropic polarizability of perturber group j, M_n^{α} is the α-component of the n-π^* magnetic dipole transition vector, $Q_n^{\beta\gamma}$ is the $\beta\gamma$-component of the n-π^* electric quadrupole transition tensor, and $\varepsilon_{\alpha\beta\gamma}$ is the Levi tensor for which the following relationships hold: $|\varepsilon_{\alpha\beta\gamma}| = 1$ if $\alpha \neq \beta \neq \gamma$ and $|\varepsilon_{\alpha\beta\gamma}| = 0$ if any two components are the same.

In evaluating Eq. (2), we assumed localized n-π^* transitions on the three carbonyl groups: C(4)–O(8), C(6)–O(9), and C(2)–O(7). The net (or total) rotatory strength associated with the degenerate set of transitions (localized on C(4)–O(8) and C(6)–O(9)) is referred to as R_1, and the rotatory strength associated with the n-π^* on C(2)–O(7) is R_2. The magnetic dipole moments of these localized transitions were taken as oriented along the C–O bonds. Coordinate origins from which X_j, Y_j, Z_j, and R_j are measured were placed on the carbonyl oxygen atoms of the three chromophoric subgroups. Perturber group polarizabilities were assigned the following approximate values [8]: $\bar{\alpha}(-CH_3) = 2.24$ Å^3, $\bar{\alpha}(-CH_2) = 1.84$ Å^3, and $\bar{\alpha}(-CH) = 1.44$ Å^3.

3.2. Structures

To assess substituent-induced optical activity in the n-π^* transitions of barbituric acid derivatives we attached a secondary butyl group to the C(5) atom and calculated n-π^* rotatory strength as a function of rotation about the C(5)–$CH(CH_3)C_2H_5$ bond. We assumed a fully extended (trans) configuration for the C(5)–$CH(CH_3)$–CH_2–CH_3 chain in each rotameric isomer. The $-CH_2$ and $-CH_3$ groups of the $-CH_2CH_3$ ligand were treated as separate perturbing groups in evaluating Eq. (2). Standard bond lengths and bond angles were assumed in calculating the positional coordinates of the atoms in the substituent group. The absolute configuration at the asymmetric carbon atom in the structures we studied is S in the Cahn-Prelog notation.

Rotation about the C(5)–C(substituent) bond is accomplished by varying the angle θ, defined as follows:



where C(4) and C(6) are ring atoms adjacent to C(5), and H^1, CH_3, and C_2H_5 are the ligand groups on the asymmetric carbon of the sec-butyl substituent. In this

Table 5. n-π^* Rotatory strengths calculated by perturbation method for (*S*)-5-(2′-butyl)barbituric acid[a, b, c]

θ	R_1	R_2	θ	R_1	R_2
0°	2.06	0.24	180	2.79	0.54
10	2.89	0.12	190	2.66	0.46
20	3.44	0	200	1.46	0.46
30	4.05	−0.07	210	−1.15	0.40
40	4.83	−0.13	220	−4.44	0.31
50	5.25	−0.18	230	−6.90	0.19
60	4.87	−0.23	240	−7.57	−0.16
70	3.86	−0.25	250	−6.91	−0.18
80	2.66	−0.29	260	−5.96	−0.21
90	1.49	−0.32	270	−5.18	−0.23
					−0.21
110	0.17	−0.48	290	−3.58	−0.18
120	0.42	−0.40	300	−2.76	−0.15
130	1.03	−0.21	310	−2.09	0.05
140	1.60	−0.11	320	−1.56	0.22
150	1.96	0.07	330	−0.99	0.25
160	2.21	0.24	340	−0.17	0.25
170	2.51	0.40	350	0.93	0.21

[a] Rotatory strengths calculated in units of $iM_n^{\alpha}Q_n^{\beta\gamma}|\varepsilon_{\alpha\beta\gamma}| \times 10^6$ cgs (see Eq. (2) in text).

[b] R_1 = algebraic sum of rotatory strengths calculated for n-π^* transitions localized on the C(4)–O(8) and C(6)–O(9) carbonyl groups.

[c] Planar trioxopyrimidine system is assumed.

Newman projection one is looking down the C(substituent)–C(5) bond. Crystal structure data on 5,5-disubstituted barbituric acid systems indicate that the bulkiest groups prefer positions above the pyrimidine ring in a plane which bisects the ring along C(5)–C(2). If this preference is also applicable to "free" molecules, then one may expect the $\theta = 180°$ conformational isomer to be preferred.

3.3. Results

The results of our perturbation calculations on the n-π^* rotatory strengths are presented in Table 5. The rotatory strengths are expressed in $iM_n^{\alpha}Q_n^{\beta\gamma}|\varepsilon_{\alpha\beta\gamma}| \times 10^6$ cgs units. The value of $iM_n^{\alpha}Q_n^{\beta\gamma}|\varepsilon_{\alpha\beta\gamma}|$ for carbonyl n-π^* transitions has been estimated to lie in the range 0.7–9.7×10^{-46} cgs units [7a]. The n-π^* transitions on the C(4)–O(8) and C(0)–O(9) carbonyl groups of (I) are not expected to be equivalent to that on the C(2)–O(7) groups. However, the value of $iM_n^{\alpha}Q_n^{\beta\gamma}|\varepsilon_{\alpha\beta\gamma}|$ is not expected to differ significantly for these three n-π^* transitions. Assuming a value of $\sim 10^{-46}$ cgs units for the spectroscopic parameter, $iM_n^{\alpha}Q_n^{\beta\gamma}|\varepsilon_{\alpha\beta\gamma}|$, the computed rotatory strengths R_1 and R_2 take on values in the range 10^{-39}–10^{-42} cgs units for the various conformation isomers of (*S*)-5-(2′-butyl)-barbituric acid listed in Table 5. These rotatory strength values are comparable in magnitude to those observed for the n-π^* transitions in asymmetrically substituted diketopiperazine systems. Additionally, according to our calculations the substituent-induced n-π^* rotatory strengths are predicted to be of the same order of magnitude as those

arising from chiral distortions within trioxopyrimidine chromophoric system (compare the results shown in Tables 4 and 5).

4. Discussion

The molecular orbital calculations performed in this study indicate that three n-π^* transitions contribute to the absorption and CD spectra of barbituric acid derivatives in the near ultraviolet region, $\lambda > 220$ nm. Two of these transitions are predicted to be nearly degenerate in energy and to be separated from the third (and higher energy) transition by ~ 0.7 eV (45 nm). All three transitions are calculated to be strongly magnetic dipole allowed, whereas the sum of the oscillator strengths calculated for these transitions is very small. Each of the three lowest energy n-π^* singlet-singlet transitions involves some charge-transfer character insofar as electron density is shifted out of localized oxygen $2p(n)$ orbitals into π^* molecular orbitals which are somewhat delocalized over all three carbonyl groups of the trioxopyrimidine chromophore. These charge-transfer processes are reflected in the data of Table 3.

Substitution at the C(5) ring atom and/or small distortions of the trioxopyrimidine moiety from planarity result in only small alterations in the oscillator strengths and transition energies computed for the three lowest lying n-π^* transitions. However, the rotatory strengths computed for these transitions are extraordinarily sensitive to C(5) substitution and to distortions within the trioxopyrimidine system (Table 4).

If we assume that the CD bands for the two lowest energy (nearly degenerate) transitions will not be resolved in solution spectra, then one expects to observe two CD bands in the region $\lambda > 220$ nm. The experimental results of Carroll and Sobti [3] reveal two strongly overlapping CD bands in this region which are both of the same sign. For the (*S*)-5-alkyl-5-(2′-pentyl)barbituric acids studied by these workers both CD bands are negative in sign and the degree to which the two bands overlap is quite sensitive to both the solvent used and the nature of the 5-alkyl substituent. In dramatic contrast to the (*S*)-5-alkyl-5-(2′-pentyl)barbituric acid compounds, the (*S*)-5-(2′-pentyl) barbituric acid compound exhibits two overlapping CD bands in the $\lambda > 220$ nm region which are both *positive* in sign. From the computed rotatory strengths displayed in Table 4 one would predict two negatively signed CD bands for the 5,5-dialkyl substituted derivatives if the predominant source of optical activity is inherent chirality within the trioxopyrimidine chromophore *and* if this chromophoric system adopts the NP1a conformational structure (see Fig. 1). Furthermore, assuming that the trioxopyrimidine moiety adopts the same (or a similar) conformational structure in the 5-alkyl substituted derivative, the results shown in Table 4 suggest that two positively signed CD bands will be observed in the $\lambda > 220$ nm region. These assignments are made based on the assumption that the first two transitions must be considered as a nearly degenerate pair whose "net" rotatory strength (that is, the algebraic sum of the individual values) governs the sign and intensity of the lowest energy CD band.

Sensitivity of n-π^* rotatory strength to the nature of the substituent group is revealed by comparing the calculated results for the 5-methyl and 5-fluoro deriva-

tives of barbituric acid (Table 4). Dependence of n-π^* rotatory strength on distortions of the trioxopyrimidine system from planarity is seen by comparing the computed results for the NP1 and NP2 isomeric forms of unsubstituted and 5-methyl substituted barbituric acid.

Since the trioxopyrimidine system is found in both planar and nonplanar conformations in various crystalline barbituric acid derivatives [1], it is not clear whether there should be a conformational preference in solution media. It is quite possible that deviations from planarity arise entirely from forces peculiar to the specific crystalline environments in which the barbiturate molecules reside. If the trioxopyrimidine moiety possesses no net inherent chirality (or dissymmetry), then the optical activity observed in the n-π^* transitions must originate with chiral centers in the substituent groups. The calculations described in section 3 were carried out to examine this source of n-π^* optical activity. The results presented in Table 5 express rotatory strength as a function of the rotation angle θ (rotation about the C(S)–C(substituent) bond) in the compound (*S*)-5-(2′-butyl)barbituric acid. The model on which these calculations were based is too crude to yield quantitatively reliable results; however, the results *should* provide *qualitatively* useful and reliable spectra-structure relationships.

Correlation between the experimental CD measurements of Carroll and Sobti [3] and the computed results shown in Table 5 requires that $300° > \theta > 240°$ for the 5,5-dialkyl compounds studied by Carroll and Sobti. Both R_1 and R_2 are computed to be < 0 within this range of values for θ. For the 5-alkyl compound studied by Carroll and Sobti, correlation between theory and experiment requires that $\theta \cong 350°$ or that θ be within one of the regions 0°–20° or 150°–200°. For these values of θ, both R_1 and R_2 are computed to be > 0. The region $300° > \theta > 240°$ allows maximal separation between the methyl and ethyl ligands of the sec-butyl substituent and the other substituent attached to C(5). If the other C(5) substituent is an alkyl group, then one may expect the region of conformational space defined by $300° > \theta > 240°$ to be favored over regions in which the alkyl substituent and the sec-butyl group are more sterically crowded. If the other C(5) substituent is hydrogen, then steric considerations do not suggest strong conformational preferences.

The hydrocarbon backbones of 5-alkyl substituents on barbituric acids are generally found to project above the plane (or near-plane) of the pyrimidine ring in the crystalline state [1]. However, a crystal structure has not yet been reported for a 5,5-dialkyl substituted barbiturate in which the substituent groups are branched. Two bulky ligands (rather than just one) on the substituent atom attached to C(5) may be expected to lead to a conformational preference defined by the $270° > \theta > 210°$ values in our model compound.

5. Summary

The results obtained in this study suggest that three singlet-singlet transitions contribute to the near ultraviolet ($\lambda > 220$ nm) absorption and optical activity spectra of chiral alkyl substituted barbituric acid derivatives. These transitions can be characterized as n-π^* excitations localized within the trioxopyrimidine

moiety. Each of these three transitions is computed to be strongly magnetic-dipole allowed and the sum of the dipole strengths (and oscillator strengths) of the three transitions is computed to be very small. Two of these three n-π^* transitions are nearly degenerate while the third lies about 0.7 eV to higher energy. The optical activity observed for these transitions can arise from: (a) chiral distortions within the trioxopyrimidine chromophore; (b) vicinal interactions between the dissymmetric alkyl substituents and a symmetric trioxopyrimidine moiety; or, (c) a combination of (a) and (b). Our calculations of the n-π^* rotatory strengths indicate that the vicinal effects and inherent chirality (within the trioxopyrimidine chromophore) can make contributions of similar magnitude. Correlations between experimental data and theoretical results may be made assuming either one or both of these sources of optical activity. These findings suggest that detailed stereochemical information on the alkyl substituted barbituric acids cannot be obtained unambiguously from chiroptical studies alone. That is, one cannot distinguish between the chiroptical effects due to substituent stereochemistry and those due to trioxopyrimidine stereochemistry. Our calculations show, however, that the near ultraviolet chiroptical observables will be extremely sensitive to very small alterations in molecular stereochemistry.

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