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CIRCULAR DICHROISM AND ELECTRONIC STRUCTURE CALCULATIONS ON NAPROXEN

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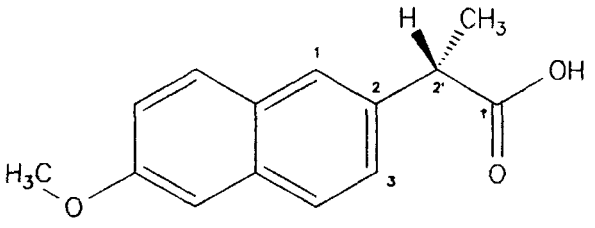
The circular dichroism (CD) spectrum of naproxen exhibits bisignate behaviour in the 210–250 nm region with pronounced temperature dependence, indicating a dynamic solution behaviour. According to semi-empirical (PM3, AM1) calculations, four conformations have to be considered in order to describe the potential energy surface of the molecule. These conformations, all chiral, differ in the relative orientation of the carboxyl group with respect to the naphthalene moiety, which could explain the differences observed in the CD spectra. Electronic structure calculations employing CNDO/S and coupled oscillator theory suggest that the two oppositely signed CD bands of naproxen are not the two components of a couplet but result from excitations of the naphthalene 1_{B_a} and 1_{B_b} states that are coupled to the carboxyl $\pi\pi^*$ transition. The four conformations are attributed to two different coupling patterns; implications with respect to observed spectra are discussed.

INTRODUCTION

Of the many derivatives of 2-arylpropionic acid that have proved effective as anti-inflammatory agents, naproxen (+)-2′-(6-methoxy-2-naphthyl)propionic acid, is one of the few that is being administered not as the racemate but as an enantiomer.[1] The compound has the *S* configuration, as was shown by chemical degradation.[2] Positive absorption in the 230 nm range of the circular dichroism (CD) spectra of several 2-arylpropionic acids including naproxen has been correlated with *S* configuration,[3] which is also the therapeutically active form. Apart from this, we are not aware of any investigations regarding the chiroptical properties of naproxen, (the inclusion complexes of naproxen with α-, β- and γ-cyclodextrin have been described,[4] but no chiroptical properties were reported) which is surprising considering the obvious relationship between absolute configuration and activity for naproxen and related arylpropionic acids.



In this work, we investigated the UV and CD spectra of naproxen between 210 and 400 nm at different temperatures and in different solvents. The CD spectra exhibit a pronounced temperature dependence, which will be shown to be intramolecular in nature and not the result of intermolecular interaction. We also performed a conformational analysis of the compound and electronic structure calculations for the most stable geometries with the aim of correlating observed spectral data with molecular conformations.

EXPERIMENTAL

Naproxen was a gift from Syntex Research (Palo Alto) and was also obtained commercially from Aldrich. The methyl ester was prepared by a standard procedure by conversion of naproxen to the acid chloride with oxalyl dichloride and reaction with methanol; m.p. 91 °C, *m/z* 185 and IR and NMR data as expected for the ester.

The solvents used were of spectral quality: methanol–ethanol (1:4, v/v); EPA [diethyl ether–isopentane–ethanol (5:5:2)] and dichloromethane. UV spectra were obtained on a Perkin-Elmer Lambda 5 spectrometer and CD spectra on a Jobin-Yvon Dichrograph Mark IV instrument, both equipped for thermocontrolled low-temperature measurements. All spectra shown have been corrected for solvent contraction.

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RESULTS

UV and CD spectra

The UV spectra of naproxen in methanol–ethanol (Figure 1) show an intense absorption with a maximum at 235 nm ($\varepsilon = 65\,000$) with a shoulder at the high-energy side, a progression of low-intensity bands at 253, 262, 272, and 283 nm ($\varepsilon = 5700$, 7300, 7800 and 4500, respectively) and two absorptions at 317 and 332 nm ($\varepsilon = 2900$ and 3700). All absorptions increase in intensity as the temperature is lowered. The spectra do not change in other solvents such as EPA or dichloromethane and the spectra of the free acid and of the methyl ester are essentially identical.

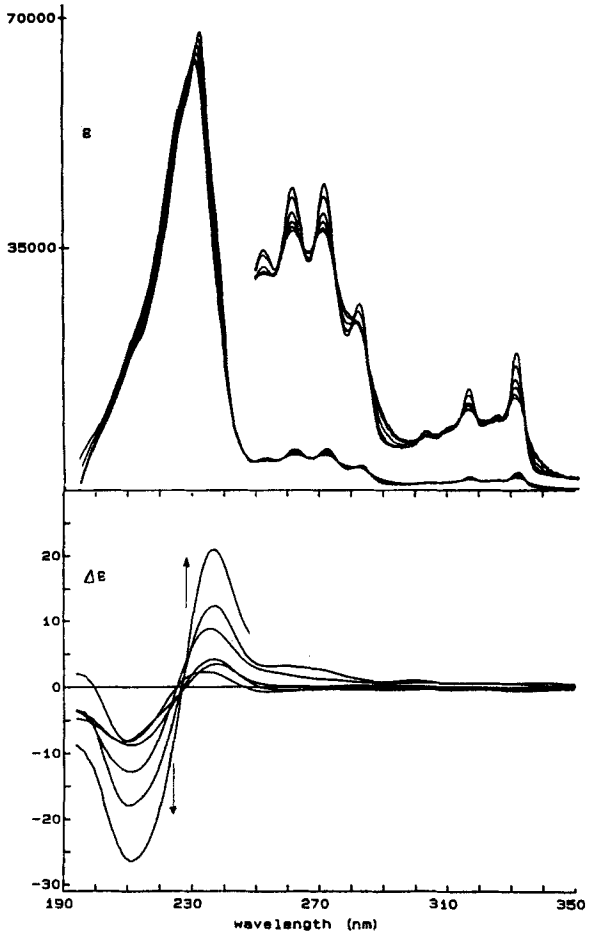


Figure 1. Temperature-dependent UV (top) and CD spectra (bottom) of naproxen in ethanol–methanol. The concentration is $1{\cdot}8 \times 10^{-3}$ M (UV) and $1{\cdot}5 \times 10^{-3}$ M (CD); for the inset in the UV spectra, divide the extinction by 7·2. The curves correspond to measurements at +20, 0, −40, −80, −120 and −160 °C. There were problems with the baseline in the CD measurement at −160 °C, so it was cut off. Arrows point into the direction of lower temperatures

The CD spectra of naproxen in methanol–ethanol are also shown in Figure 1. In contrast to the UV spectra they show a distinct temperature dependence, with a negative band developing at 210 nm and a positive band at 235 nm. The amplitudes reached at 160 °C are −28 and +22 $\Delta\varepsilon$, respectively. The spectra taken in the non-polar solvent EPA (not shown) differ from the methanol–ethanol spectra only at higher temperatures where the seemingly bisignate structure is more pronounced than in methanol–ethanol.

The spectra are not dependent on concentration, which makes it unlikely that aggregates, such as cyclic hydrogen-bonded dimers, are responsible for these spectra. In order to rule out this possibility completely, the methyl ester of naproxen was prepared and its spectra obtained under identical conditions. The methanol–ethanol spectra (not shown) have a larger amplitude but otherwise they are essentially identical with the spectra of the free acid.

Treatment of naproxen with trifluoroacetic acid (TFA) should yield the protonated acid, but the spectra of this species proved difficult to obtain. Naproxen is insoluble in hydrocarbon solvents, and in mixtures such as EPA addition of TFA results in at least partial protonation of the solvent. Dichloromethane, on the other hand, does not allow spectroscopy below 220 nm. The CD spectra of naproxen–TFA in dichloromethane and in EPA are shown in Figure 2. Protonation results in a red shift of the positive CD band, to about 240 nm, with a pronounced increase in amplitude at lower temperatures. In addition to the negative band at 210 nm

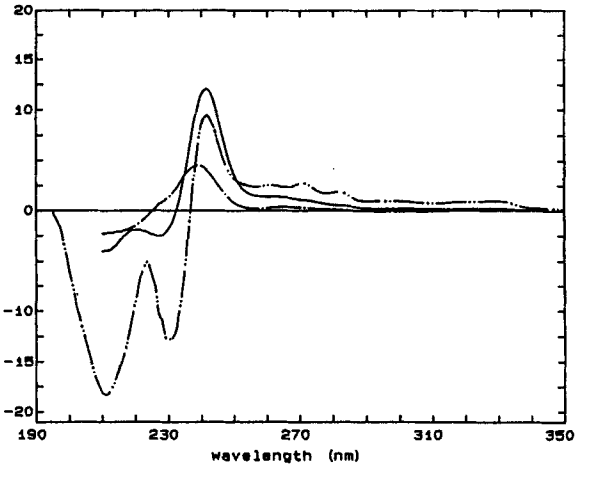


Figure 2. CD spectra of naproxen–TFA in dichloromethane at +20 (—·—·—) and −80 °C(————) and in EPA at −160 °C (—··—··). The naproxen concentration is 6×10^{-3} M, with an approximately five-fold excess of TFA

there is another one at 230 nm. We cannot rule out the possibility that this spectrum is really the superposition of two spectra, one corresponding to the free acid and the other to the protonated species.

Conformational analysis

The spectral data presented in the preceding section suggest a temperature-dependent dynamic equilibrium between different chiral conformations of naproxen. This appears reasonable: one can think of the naproxen molecule as being composed of two formally isolated chromophores that can be rotated independently about single bonds and whose relative disposition is always chiral.

Leaving aside the rotation of the methoxy group, which can be assumed to have only a minor influence on the electronic spectra of the molecule, the conformation of naproxen can be specified by the dihedral angles of just two bonds, viz. those connecting the asymmetric carbon with the naphthalene group on one and the carboxyl group on the other side. We have calculated the potential energy of naproxen as a function of these two dihedral angles, C(3)—C(2)—C(2′)—H and O=C(1′)—C(2′)—H. A 0° dihedral angle corresponds, for the rotation of the naphthyl group, to the conformation in which the C(2′)—H bond is eclipsed with the naphthalene C(2)—C(3) bond. For the carboxyl group, on the other hand, 0° corresponds to an eclipsed arrangement of the C(2′)—H bond and the C=O bond. Calculations were performed in which these two angles were varied independently in 5° increments over the whole range of 360°. By treating these angles as independent (which they are not, of course, in reality), we avoid creating an excessively large data file containing the coordinates of $(360/5 - 1)^2$ different conformations, most of which, it will turn out, are of no relevance to our analysis anyway because of their high energy.

Rotation of the naphthyl group involves a twofold barrier that was calculated with PM3 (PM3 and AM1 are part of the MOPAC package[5]) and is shown in Figure 3. Each data point corresponds to a completely optimized geometry of the naproxen molecule, the only fixed parameter being the value of the dihedral angle indicated on the abscissa. Naphthyl rotation can start from either of the two most plausible conformations for the carboxyl group: in that shown it is 180° and in the other it is 0°. Figure 3 shows that the interaction between the two chromophores is small, the carboxyl group preferring throughout an orientation which is almost independent of the orientation of the naphthyl group.

The odd appearance of the potential energy function shown in Figure 3, especially the indented maxima and the splitting of the minima, is an artefact of PM3 that we have encountered before and have drawn attention to elsewhere:[6] under certain conditions, viz. when there is the possibility of close contact between non-bonded hydrogens at a distance around 180 pm, PM3 will cal-

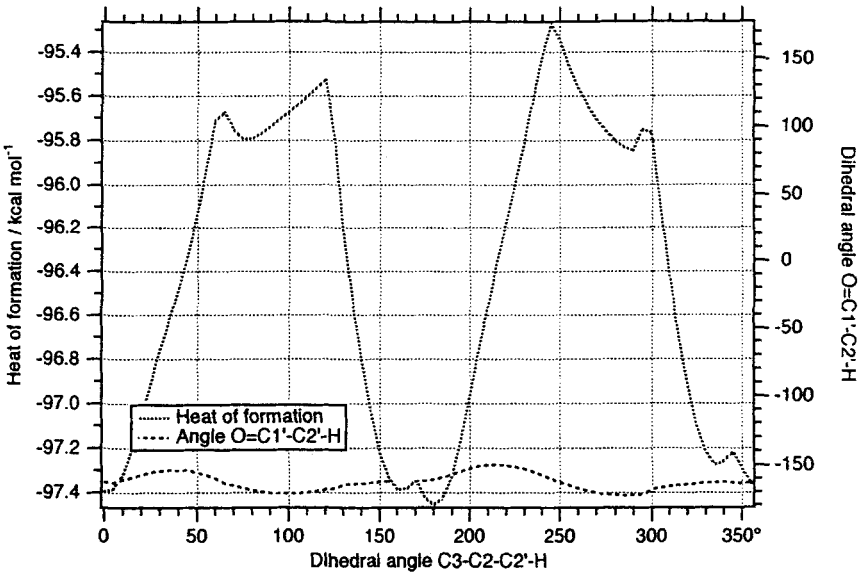


Figure 3. PM3-calculated energy of naproxen as a function of the dihedral angle C(3)—C(2)—C(2′)—H (rotation of the naphthyl group). For a discussion of the irregular shape of the curve, see text. The curve at the bottom indicates the movement of the carboxyl group as the naphthyl group rotates

culate structures with energies much too negative. We have checked the conformations corresponding to the 'sawn-off' maxima and found such close contacts between the C(3) hydrogen and one of the hydrogens of the methyl group.

AM1 does not suffer from this deficiency; a recalculation of the naphthyl rotation with this method yields smooth barriers, with no unexpected drops or dents. Another example for an AM1 calculation is shown in Figure 4, in which the carboxyl group is rotated around the C(1′)—C(2′) bond. Starting with the two favoured orientations of the naphthyl ring suggested by the results in Figure 3 (of which only one is shown), this barrier is seen to be twofold also. The conformation with a 190° dihedral angle (this corresponds to a geometry in which the C(2′)—H bond is in an almost eclipsed orientation with respect to the carboxyl C—OH bond) is significantly more stable, by 0·6 kcal mol^{-1} (1 kcal = 4·184 kJ), than that in which this bond eclipses the C=O bond. A similar effect has been reported in an STO-3-21G study of the rotational barrier of isobutyric acid: all conformations in which hydrogen is on the side of the carboxyl C—O group are favoured, by about 1 kcal mol^{-1}, relative to those where it is on the sides of C=O.[7] In contrast, the two minimum energy conformations of the naphthyl group [C(2′)—H eclipsed with C(3)—H vs C(1)—H] differ by less than 0·1 kcal mol^{-1}. The barrier to rotation of the carboxyl group is 2·0 or 2·4 kcal mol^{-1} depending on the starting geometry.

As a result of the calculations, we find four plausible geometries corresponding to the combination of each of the two minimum energy values of one dihedral angle with both minimum energy values of the other. These four geometries were then completely re-optimized without any restraint. The resulting structures are shown, together with energies and values of the two relevant dihedral angles, in Figure 5. The energies are very close the calculated difference between the most stable (d) and the least stable conformmation (a) being less than 0·7 kcal mol^{-1}. They all present local minima, their interconversion via naphthyl or carboxyl rotation requiring of the order of 2 kcal mol^{-1}.

In all four conformations the C(2′)—H bond is almost eclipsed with the planes of the naphthalene and the carboxyl group, an arrangement that is obviously favoured for steric reasons. Exact eclipsing is not achieved because of the asymmetry of C(2′). Of the two possibilities of rotating away from the naphthalene plane, that realized in all conformations is the one that leaves the methyl group with more space than the carboxyl group. This is understandable since the latter can rotate away from the aromatic system while the former cannot because of its rotational symmetry. With respect to the carboxyl group, the two most stable conformations have the C(2′)—H bond on the side of the C—OH bond, with rotation from exact eclipsing again in that direction which gives the methyl group more space than the naphthyl group, probably for the same reason as pointed out above.

A comparison with the crystal structure of naproxen[8] can be only partly relevant. The observed hydrogen

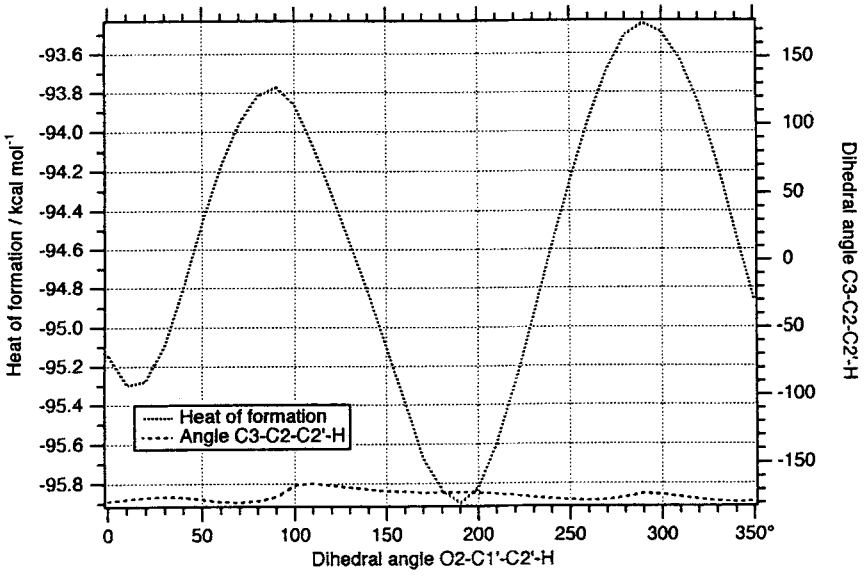
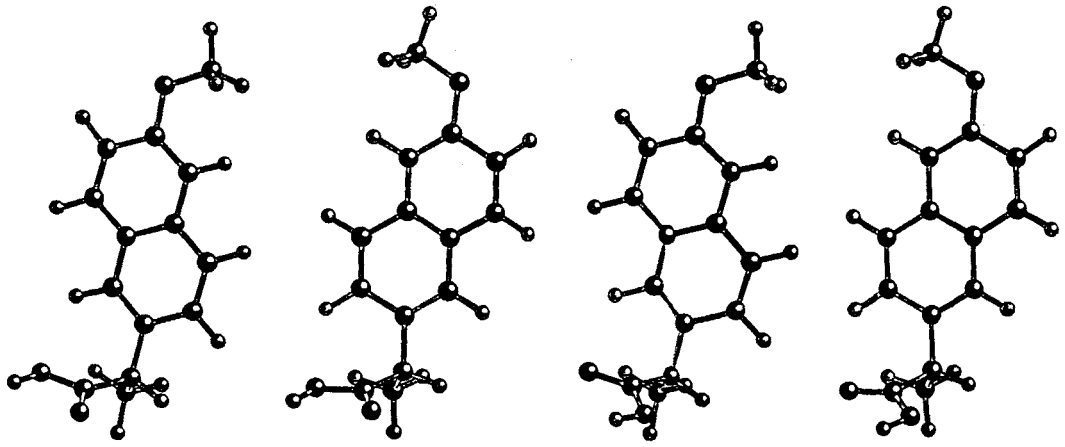


Figure 4. AM1-calculated energy of naproxen as a function of the dihedral angle O=C(1′)—C(2′)—H (rotation of the carboxyl group). The curve at the bottom describes the movement of the naphthyl group as the carboxyl group rotates



Conformation	a	b	c	d
Heat of form./ kcal mol^{-1}	-95.21	-95.29	-95.53	-95.90
Dihedral C3-C2-C2'-H	6.5°	-175.8°	12.2°	-171.9°
Dihedral O=C1'-C2'-H	12.1°	13.7°	-172.5°	-170.4°

Figure 5. Plot of the four lowest energy conformations of naproxen. Also given are the (AM1) calculated heats of formation and the values of the two dihedral angles specifying the relative orientation of the naphthyl and the carboxyl group, respectively

bonding between neighbouring molecules in the crystal lattice tends to equalize the C=O and the C−OH bond of the carboxyl group; also, packing effects of the large naphthalene units may well force the molecule into a special crystal conformation. The orientation of the carboxyl group [153° for the dihedral angle O=C(1')−C(2')−H] differs considerably from that which we calculate in any of the conformations; the corresponding angle of the naphthalene group [C(3)−C(2)−C(2')−H] is −175°.

In conclusion, we have found four well defined conformations of naproxen accessible via single-bond rotation. The close energy of these conformations and their easy interconversion make it imperative to consider all four of them when discussing the electronic spectra of the compound.

Electronic structure calculations

The conformational flexibility of the molecule of which the CD spectra appear to be a manifestation is a consequence of the unhindered rotations about the two single bonds joining the naphthyl and the carboxyl unit via the asymmetric carbon atom. These two bonds formally isolate those two chromophores, which suggests a theoretical model for the description of the excited states of the molecule, viz. in terms of coupled oscillators. According to this model,[9] the excited states of the molecule are expressed as linear combinations of the excited states of the single chromophores whose interaction is calculated classically from the coulombic interaction between the respective transition densities. Diagonalization of the interaction matrix yields the energies of the coupled states with the corresponding eigenvectors representing the coupling modes of the chromophores.

For a description of the isolated chromophores, CNDO/S was employed, from which dipoles representing the transition densities and energies were transferred into the interaction routines. The results for the 2-methoxynaphthalene chromophore are summarized in Table 1, together with calculated results for naphthalene. There is a close correspondence between the results as expected because the methoxy group exerts only a minor perturbing effect. The four fundamental absorptions, ^1L_b, ^1L_a, ^1B_b and ^1B_a, that characterize the naphthalene excited states can be correlated with four states with very similar charge distributions in the substituted naphthalene, with of course polarizations no longer along the short and long axes of the naphthalene skeleton but slightly rotated as a result of the substitution. The remaining three states containing large contributions from oxygen lone pair excitations have low oscillator strengths and will turn out to be of minor importance for the naproxen excitations. The agreement with experiment is satisfactory for both

Table 1. CNDO/S-calculated wavelengths (experimental values[a] in italics) and oscillator strengths of naphthalene and 2-methoxynaphthalene and corresponding symmetry designations

	Naphthalene			2-Methoxynaphthalene		
State	Wavelength (nm)		f	Wavelength (nm)		f
^1L_b	306	(*312*)	0·006	310	(*330*)	0·009
^1L_a	269	(*289*)	0·177	272	(*285*)	0·154
^1B_b	221	(*220*)	1·844	226	(*235*)	1·758
				226		0·188
				215		0·068
^1B_a	204	(*190*)	0·676	211		0·625
				189		0·013

[a] Experimental assignments for naphthalene, Refs. 10–12, and for 2-methoxynaphthalene, Refs. 13 and 14.

molecules. For 2-methoxynaphthalene the correct relative energies of the predominantly long-axis polarized ^1B_b[13] and the short-axis polarized ^1B_a state will turn out to be especially important in the application of coupled oscillator theory.

For a description of the carboxyl group, similar calculations were performed on propionic acid, yielding two states, at 282 nm ($f = 0·001$) and 132 nm ($f = 0·511$), corresponding to the $n\pi^*$ and the $\pi\pi^*$ excitations, respectively.

Calculations for the molecule as a whole employing the same CNDO/S formalism (Table 2) indicate that the excited states of naproxen can indeed be described as resulting from the interaction between the naphthalene and the carboxyl excited states. From the transition densities the four aromatic states discussed above are clearly discernible as is the carboxyl $n\pi^*$ state (the carboxyl $\pi\pi^*$ excitation is too high in energy and does not play a significant role in the CI calculation). The CI state 4 is an exception in that it contains a large admixture of the antibonding π^* orbital of the carboxyl group combined with a complicated mixture of coefficients in the naphthyl group. Because of the very small value of the oscillator strength, this state can be neglected for spectral assignments.

Table 2. CNDO/S-calculated wavelengths, oscillator strengths and parentage of naproxen excited states

CI state	Wavelength (nm)	f	Composition
1	317	0·023	^1L_b, naphthalene
2	276	0·175	^1L_a, naphthalene
3	248	0·126	^1L_b, naphthalene; $n\pi^*$, carboxyl
4	230	0·005	naphthalene; $\pi\pi^*$, carboxyl
5	225	1·886	^1B_b, naphthalene
6	212	0·721	^1B_a, naphthalene
7	—	—	$\pi\pi^*$, carboxyl[a]

[a] CNDO/S value not calculated.

According to these calculations, the UV absorptions of naproxen at 330, 270 and 232 nm and the shoulder at 215 nm (Figure 1) are essentially the naphthalene ^1L_b, ^1L_a, ^1B_b and ^1B_a excitations; the carboxyl $n\pi^*$ excitation around 250 nm could be hidden or could even be the main component of the vibronic band system extending from 250 to 280 nm.

In contrast to ordinary absorption, the circular dichroism of a molecule is highly dependent on the molecular conformation. The reason is well known: while the oscillator strength is proportional to the square of the electric transition moment (and thus a function only of the absolute value of this moment), rotatory strengths are a function of both the electric and the magnetic moments and the angle subtended by them. This geometry dependence enters the coupled-oscillator model via the distance-dependent off-diagonal matrix elements that are calculated as the coulombic interaction of the oscillators representing the electronic transition densities of the isolated chromophores.

For the calculations, all seven excited states of 2-methoxynaphthalene (Table 1) and the two propionic acid states described in the text were approximated by extended dipoles with energy, length, origin and orientation fitted to the results of the CNDO/S—CI calculations of the isolated chromophores. The procedure for this has been described in detail elsewhere.[15] The results are given in Table 3.

Rotatory strength, according to Table 3, is predominantly the result of the pairwise interaction of the naphthalene ^1B_a and ^1B_b and the carboxyl $\pi\pi^*$ excited states, the other interactions yielding small or (in case of the conformations c and d) even negligible contributions. In orders of magnitude the calculated rotatory strengths agree with measured values [$\pm 50 \times 10^{-40}$ cgs] (approximate values obtained by multiplying $\Delta\varepsilon_{max}$ by $2·55 \times 10^{-40}$)[16]. It also suggests

Table 3. Calculated oscillator[a] and rotatory strengths (in 10^{-40} cgs)[b] for the four conformations in Figure 5

Wavelength (nm)	Oscillator strength	Rotatory strength a	b	c	d
272	0·15	5	4		
226	0·13	2	−3		
223	1·89	−15	−54	20	16
215	0·05	−1			
210	0·67	21	22	−3	−6
131	0·50	−11	30	−17	−11

[a] The values correspond to conformation a; calculated oscillator strengths for the other conformations do not differ significantly from these, so they are not quoted separately.
[b] Only states with $R > 10^{-40}$ cgs are considered.

that coupling with the $\pi\pi^*$, not with the $n\pi^*$, excited state of the carboxyl group is responsible for the observed CD; this is corroborated by the fact that the strong CD absorptions survive protonation of naproxen, a process which will mostly affect the $n\pi^*$ state.

Since the two naphthalene excitations are almost perpendicular (^1B_a is predominantly short- and ^1B_a long-axis polarized), it is easy to understand that interaction with a third common chromophore will yield coupled states with opposite rotatory strengths. There is a pairwise differentiation between the four conformations: a and b give a $\pm$ pattern for the 223 and the 210 nm absorptions, whereas for c and d this pattern is the reverse. Whereas for the spectrum as a whole the sum rule[9] is fulfilled, as it should be in this closed system, it does not hold for the two absorptions just mentioned because they are caused, according to our calculations, by different interactions. From the appearance of the spectrum, one would have expected otherwise: the symmetrical shape of the CD-curve, with a simultaneous increase in the negative and the positive band with decrease in temperature, is typical for exciton interaction between two chromophores and the emergence of a favoured conformation at lower temperature.

There are no chromophores in naproxen of sufficient intensity and flexible relative orientation that could cause the appearance of such an exciton couplet, so the (approximate) symmetry of the CD curve must be considered accidental. This is in line with the calculations that yield opposite signs for the two bands but of different magnitude. This is especially true for the two low-energy conformations c and d in which the absorption at 210 nm attains only one seventh to one fifth of the rotatory strength of the absorption at 223 nm. The argument that at low temperature these conformations predominate because the (calculated) $\pm$ pattern of the CD bands agrees with the experimental CD spectrum loses some of its force because of the small value of the calculated 210 nm rotatory strength.

CONCLUSION

The conformational analysis of naproxen has yielded four different structures that can be interconverted by single-bond rotations. The energies of these conformations are so close that a definite assignment as to the preferred state in solution cannot be made. Calculated excited states and oscillator strengths allow an assignment of the UV spectrum of naproxen and its correlation with the spectrum of naphthalene and methoxynaphthalene. The energetically close and intense ^1B_b and ^1B_a states at 223 and 210 nm, respectively, couple with the carboxyl $\pi\pi^*$ excitation to give two states of opposite rotatory strengths that are responsible for the two oppositely signed absorptions in the CD spectrum of naproxen. The temperature dependence of these absorptions is indicative of the dynamic equilibrium between different conformations; the agreement of the experimental sign pattern in the CD with that calculated for the two lowest energy conformations must at least in part be considered fortuitous.

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