

## Discussion

These results continue to support the hypothesis that to a first approximation electrochemistry of an electrode-immobilized chemical can be anticipated from that of its dissolved counterpart. Exceptions arise, and in the present case they are provoked by use of a poorly solvating medium. It is of interest to note in this connection that solubility of a redox couple, once immobilized on the chemically modified electrode surface, is no bar to experimentation, but observed electrochemical properties may then reflect specific surface effects.

Two aspects of detailed structure of carbon-bonded tetra(aminophenyl)porphyrin were revealed in that two amide bonds form, on the average, with the carbon, and that axial sites in bonded CoT(NH<sub>2</sub>)PP are open for coordinative attack. These two features are consistent with the hypothesis that stable chemically modified surfaces are amenable to predictive electrocatalysis.<sup>21</sup>

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## References and Notes

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- (9) We have confirmed the uncompensated cell resistance dependency described by Anson,<sup>5</sup> and also observe additional sensitivity enhancement at shortened pulses (e.g., 0.1 s/pulse) and via the peak current-pulse amplitude (5–100 mV) proportionality.
- (10) Representing the faradaic pseudocapacitance as  $C_f$ , and using a fast charge transfer equivalent circuit model,<sup>5</sup> the ac response to  $\Delta E \sin(\omega t)$  excitation is

$$i_{ac} = \frac{\Delta E \omega (C_{dl} + C_f)}{[1 + \omega^2 R_u^2 (C_{dl} + C_f)^2]^{1/2}} \sin(\omega t + \phi)$$

where  $\tan \phi = [\omega R_u (C_{dl} + C_f)]^{-1}$ . When  $C_f \gg C_{dl}$ ,  $\omega R_u C_f < 1$ , and  $C_f$  invariant over  $\Delta E$  (so  $\phi = 90^\circ$ );  $i_{ac} = \Delta E \omega C_f$ , and  $(i_{ac})_{max}$  occurs at  $(C_f)_{max}$  which is at  $E^{0'}$ .

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## Optically Active Amines. 24.<sup>1</sup> Circular Dichroism of the Para-Substituted Benzene Chromophore<sup>2</sup>

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**Abstract:** Para substitution of chiral norephedrine causes the sign of the <sup>1</sup>L<sub>b</sub> Cotton effects, negative for (αR)-norephedrine and positive for (αR)-norpseudoephedrine, to be opposite from that of the unsubstituted parent. This reversal is due to the sign change in the rotatory contribution of the chiral center adjacent to the benzene chromophore. The contribution can be subdivided into static (one-electron) as well as dynamic (coupled oscillator) mechanisms. In the unsubstituted compounds, the one-electron mechanism is dominant. On para substitution, the transition moments become larger resulting in the opposite signed contribution of the coupled oscillator mechanism overshadowing that of the one-electron mechanism. Similar considerations may also be applied to explain the sign changes on para substitution of other related chiral compounds: mandelic acid, β-hydroxy-β-phenylpropionic acid, N-(dichloroacetyl)norephedrine, and α-phenylethylamine. This analysis clearly indicates, however, that no single universally applicable sector rule can be devised for the prediction of the <sup>1</sup>L<sub>b</sub> Cotton effects of the benzene chromophore since the one-electron and the coupled oscillator mechanisms by which the observed Cotton effects are generated make rotatory contributions of approximately equal magnitude. It appears that for open-chain chiral substituents with ε < 100, the one-electron mechanism is dominant. With ε > 200, the coupled oscillator mechanism may be more important.

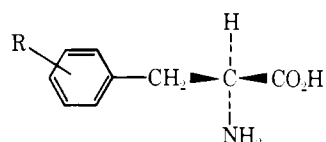
Snatzke, Kajtar, and Warner-Zamojska<sup>5</sup> proposed a sector rule based on the nodal planes of the benzene ring and Platt's spectroscopic moments<sup>6,7</sup> by which the direction of the overall spectroscopic moment vector is used to predict the relative sign of the <sup>1</sup>L<sub>b</sub> Cotton effects of chiral benzene compounds after ring substitution. In the case of a single added substituent, the rule predicts that for the ortho- and meta-substituted compounds the sign of the <sup>1</sup>L<sub>b</sub> Cotton effects will be opposite to that of the parent and the para-substituted analogue if the spectroscopic moments of the original chiral group and of the added substituent are of the same sign and approximate magnitude. Experimental agreement with this prediction was noted by Snatzke<sup>5</sup> with the substituted phen-

ylalanines. Both L-phenylalanine<sup>8,9</sup> (L-1a) and L-tyrosine<sup>8,10</sup> (L-1b) show a positive circular dichroism (CD) band at about 260 nm (<sup>1</sup>L<sub>b</sub>) while the corresponding band for L-o- and L-m-hydroxyphenylalanine (L-1c and L-1d) is negative.<sup>10</sup> However, observations with mandelic (2, R = H) and ring-substituted mandelic acids<sup>11</sup> (2) do not agree with the prediction. Snatzke<sup>5</sup> attributed this failure to a change in rotamer population as a result of substitution, the ring substituent affecting the hyperconjugation of the chiral group with the benzene system. More recently, similar failures of the rule have been encountered when the CD spectrum of β-hydroxy-β-phenylpropionic acid (3, R = H) is compared with those of its halogen-substituted derivatives (3).<sup>12</sup> The sign of the <sup>1</sup>L<sub>b</sub>

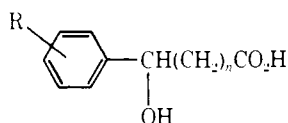
Table I. Chiral  $\beta$ -Phenylalkylamine Hydrochlorides and  $\beta$ -Phenylalkylamines Used

Compd	Name	$[\alpha]^{25}_D$ , deg <sup>a</sup>	Ref <sup>b</sup>
( <i>S</i> )- <b>5a</b>	( <i>S</i> )- $\alpha$ -Benzylethylamine hydrochloride	+21.6	17
( <i>S</i> )- <b>8a</b>	( <i>S</i> )- $\alpha$ -( <i>p</i> -Chlorobenzyl)ethylamine hydrochloride	+21	18
( <i>R</i> )- <b>10a</b>	( <i>R</i> )- $\alpha$ -( <i>p</i> -Hydroxybenzyl)ethylamine hydrochloride	-26	<i>c</i>
( <i>S</i> )- <b>11a</b>	( <i>S</i> )- $\alpha$ -( <i>p</i> -Aminobenzyl)ethylamine dihydrochloride	+16	18
( $\alpha R, \beta S$ )- <b>12a</b>	( $\alpha R$ )-Norephedrine hydrochloride	+32	18
( $\alpha R, \beta S$ )- <b>13a</b>	( $\alpha R$ )- <i>p</i> -Chloronorephedrine hydrochloride	+35	18
( $\alpha R, \beta S$ )- <b>14b</b>	( $\alpha R$ )- <i>p</i> -Hydroxynorephedrine	+17 <sup>d</sup>	19
( $\alpha S, \beta S$ )- <b>15a</b>	( $\alpha S$ )-Norpseudoephedrine hydrochloride	+43	18
( $\alpha R, \beta R$ )- <b>16a</b>	( $\alpha R$ )- <i>p</i> -Chloronorpseudoephedrine hydrochloride	-39	18
( $\alpha S, \beta S$ )- <b>17a</b>	( $\alpha S$ )- <i>p</i> -Hydroxynorpseudoephedrine hydrochloride	+76.1	19
( $\alpha S, \beta S$ )- <b>17b</b>	( $\alpha S$ )- <i>p</i> -Hydroxynorpseudoephedrine	+88 <sup>d</sup>	19

<sup>a</sup> *c* 0.5–9.0 g/100 mL of water or as noted otherwise. <sup>b</sup> For source and/or characterization. <sup>c</sup> This work. <sup>d</sup> Methanol as solvent.

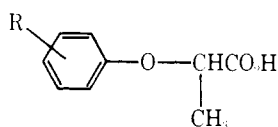


L-1a, R = H  
L-1b, R = *p*-OH  
L-1c, R = *o*-OH  
L-1d, R = *m*-OH



**2**, *n* = 0; R = H, F, Cl, Br, or OCH<sub>3</sub>  
**3**, *n* = 1; R = H, F, Cl, or Br

Cotton effects of  $\alpha$ -phenoxypropionic acid (**4**, R = H) is unchanged when the ring is substituted at the ortho, meta, and para positions with a methoxy group (**4**).<sup>13</sup>

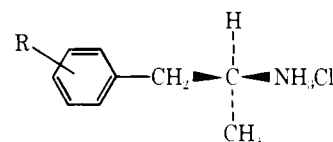


**4**, R = H or OCH<sub>3</sub>

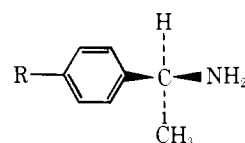
In order to rationalize the CD spectra of the ring-substituted mandelic acids, the conformational preference of these compounds was examined in some detail.<sup>14</sup> Except for the ortho isomers, no great differences in preferred conformation were found. Using more precise spectroscopic moments for the substituents, the signs of the experimentally observed <sup>1</sup>L<sub>b</sub> Cotton effects were made more, but not completely, consistent with predictions based on Sneath's rule.<sup>14</sup>

For compounds with the chiral center separated from the ring by a methylene group as in **1**, it was originally concluded by Sneath that the conformational equilibrium of the chiral group about its attachment bond to the benzene ring should not depend to any great extent on ring substitution, since hyperconjugation of the chiral group with the ring is less affected.<sup>5</sup> Compounds of this type should then conform to the rule.

To verify this latter conclusion, we compared the CD of (*S*)- $\alpha$ -benzylethylamine hydrochloride [(*S*)-**5a**] and the free base [(*S*)-**5b**] with those of the *o*-, *m*-, and *p*-chloro analogues (**6a–8a** and **6b–8b**).<sup>15</sup> These substances are well suited for this purpose in that the spectroscopic moment of a chloro and of a methyl substituent are nearly identical in sign and magnitude.<sup>6,7</sup> Contrary to prediction, however, the sign of the <sup>1</sup>L<sub>b</sub> Cotton effects is the same (positive) for the unsubstituted [(*S*)-**5a**] and the meta-substituted [(*S*)-**7a**] compounds. The rule is obeyed in that the ortho-substituted derivative [(*S*)-**6a**]



(*S*)-**5a**, R = H  
(*S*)-**6a**, R = *o*-Cl  
(*S*)-**7a**, R = *m*-Cl  
(*S*)-**8a**, R = *p*-Cl  
(*S*)-**10a**, R = *p*-OH  
(*S*)-**11a**, R = *p*-NH<sub>3</sub>Cl



(*S*)-**9a**, R = H  
(*S*)-**9b**, R = CH<sub>3</sub>, OCH<sub>3</sub>, Cl, or Br  
(*S*)-**9c**, R = CN

has <sup>1</sup>L<sub>b</sub> Cotton effects of the opposite sign while those of the para-substituted compound [(*S*)-**8a**] are of the same sign as those of (*S*)-**5a**. The same is true for the respective free bases which have CD spectra not greatly different from those of the respective salts.

These experimental observations, however, do not completely invalidate Sneath's rule since the possibility of some conformational alteration with ring substitution exists. This is especially true for ortho substitution and to a lesser extent with meta.<sup>14</sup> A good test of Sneath's rule should be the comparison of the <sup>1</sup>L<sub>b</sub> Cotton effects of unsubstituted and para-substituted compounds whose conformational distribution is not expected to change drastically as the result of substitution. Such a systematic study was done by Gottarelli and Samori<sup>16</sup> with (*S*)- $\alpha$ -phenylethylamine [(*S*)-**9a**] and various para-substituted derivatives [(*S*)-**9b** and (*S*)-**9c**]. Except for the *p*-cyano derivative (*S*)-**9c**, the <sup>1</sup>L<sub>b</sub> Cotton effects of the para-substituted derivatives [(*S*)-**9b**] are opposite in sign to that of the parent amine, although, except for the cyano group which has a large, opposite spectroscopic moment, the substituents have spectroscopic moments of the same sign as that of the chiral substituent. Thus the experimental results are in complete disagreement with predictions by Sneath's rule. Gottarelli and Samori<sup>16</sup> attempted other interpretations without success.

As a continuation of these considerations we now report the chiroptical properties of the  $\beta$ -phenylalkylamine hydrochlorides shown in Table I and analyze the factors which give rise to the Cotton effects associated with the respective <sup>1</sup>L<sub>b</sub> transitions. Except for (*R*)-**10a**, these substances were prepared and/or characterized in connection with other work.<sup>17–19</sup> The

**Table II.** Spectral Data for  $\beta$ -Phenylalkylamine Hydrochlorides in Methanol<sup>a</sup>

Compd	Spectrum	Max. $\lambda$ , nm ( $\epsilon^b$ or $[\theta]^c$ )							Cutoff $\lambda$ , nm ( $[\theta]^c$ )
		<sup>1</sup> L <sub>b</sub> <sup>d</sup>					<sup>1</sup> L <sub>a</sub>		
		a <sub>1</sub>	b <sub>2</sub>	a <sub>1</sub>	b <sub>2</sub>	a <sub>1</sub>			
		$ (4-6) \times 10^2 \text{ cm}^{-1} \rightarrow  $	$ (7-10) \times 10^2 \text{ cm}^{-1} \rightarrow  $	$ (7-12) \times 10^2 \text{ cm}^{-1} \rightarrow  $	$ (9-12) \times 10^2 \text{ cm}^{-1} \rightarrow  $				
( <i>R</i> )- <b>5a</b> <sup>e,f</sup>	UV	267 (80)	264 (120) <sup>g</sup>	261 (120) <sup>g</sup>	258 (170)		207 (7800)		
	CD	268 (-210)		262 (-230)		254 (-160)	215 (-8800)		
( <i>R</i> )- <b>8a</b> <sup>e,f</sup>	UV	276 (240)		268 (280)		261 (220)	224 (9500) <sup>g</sup>	220 (11 000)	
	CD	277 (-160)		268 (-170)		262 (-140)	227 (-13 000)	223 (-9000)	
( <i>R</i> )- <b>10a</b>	UV	284 (1300) <sup>g</sup>		277 (1600)			224 (8000)		
	CD			277 (-350)				247 (-280)	
( <i>R</i> )- <b>11a</b> <sup>e</sup>	UV <sup>h</sup>	268 (120)	264 (160)		259 (220)			255 ( $\pm$ 0)	
	CD	268 (-140)		261 (-120)					
( $\alpha R, \beta S$ )- <b>12a</b>	UV	267 (79) <sup>g</sup>	264 (160)	260 (130) <sup>g</sup>	257 (200)		208 (8000)		
	CD	268 (-720)		261 (-790)		255 (-490)		219 (+240)	
( $\alpha R, \beta S$ )- <b>13a</b>	UV	275 (180)	270 (160) <sup>g</sup>	267 (240)		260 (200)	224 (9500) <sup>g</sup>	220 (11 000)	
	CD	275 (+150)		268 (+150)		262 (+90)		228 (+400)	
( $\alpha R, \beta S$ )- <b>14a</b>	UV <sup>i</sup>	282 (1400) <sup>g</sup>		276 (1600)					
	CD <sup>i</sup>	285 (+500)		279 (+500)				233 (+480)	
( $\alpha R, \beta R$ )- <b>15a</b> <sup>e</sup>	UV	267 (73) <sup>g</sup>	264 (160)	261 (120) <sup>g</sup>	257 (200)		208 (7800)		
	CD	268 (+280)		261 (+310)		255 (+220)		220 (-190)	
( $\alpha R, \beta R$ )- <b>16a</b>	UV	275 (180)	270 (180) <sup>g</sup>	266 (230)		259 (200)	224 (9900) <sup>g</sup>	220 (12 000)	
	CD	275 (-300)		268 (-300)		262 (-180)		228 (+710)	
( $\alpha R, \beta R$ )- <b>17a</b> <sup>e</sup>	UV	283 (1100)		276 (1400)			226 (8900)		
	CD	283 (-700) <sup>g</sup>		277 (-760)			223 (-6500)	218 (-4900)	
<b>18</b>	UV	271 (180)	267 (150) <sup>g</sup>	264 (240)	261 (190)	257 (190)			
<b>19</b>	UV <sup>i</sup>	264 (58) <sup>g</sup>	261 (130)		254 (170)				

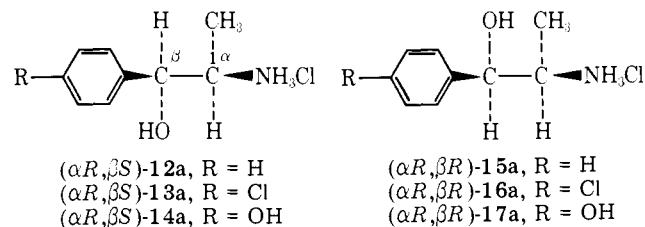
<sup>a</sup> For previously unreported CD spectra,  $c$   $3.12 \times 10^{-3}$  to  $9.29 \times 10^{-2}$  g/100 mL; length 1 cm; temperature 25–58 °C. <sup>b</sup> Molar absorptivity. <sup>c</sup> Molecular ellipticity. <sup>d</sup> Additional UV and CD maxima were usually observed at shorter wavelength. No sign inversion of the maxima at shorter wavelength was observed in any CD spectrum. <sup>e</sup> Enantiomer used. <sup>f</sup> UV and CD spectra from ref 15. <sup>g</sup> Shoulder. <sup>h</sup> Hydrochloride examined in dilute methanolic hydrogen chloride. <sup>i</sup> Free base examined in dilute methanolic hydrogen chloride.

Table III. Spectral Data for  $\beta$ -Phenylalkylamines in Methanol<sup>a</sup>

Compd	Spectrum	Max. $\lambda$ , nm ( $\epsilon^b$ or $[\theta]^c$ )					Cutoff $\lambda$ , nm ( $[\theta]^c$ )
		<sup>1</sup> L <sub>b</sub> <sup>d</sup>					
		a <sub>1</sub>	b <sub>2</sub>	a <sub>1</sub>	b <sub>2</sub>	a <sub>1</sub>	
		$-(4-6) \times 10^2 \text{ cm}^{-1} \rightarrow$		$(9-10) \times 10^2 \text{ cm}^{-1} \rightarrow$			
		$(7-11) \times 10^2 \text{ cm}^{-1} \rightarrow$		$(7-12) \times 10^2 \text{ cm}^{-1} \rightarrow$			
(R)-5b <sup>e</sup>	UV <sup>f</sup>	268 (120)	264 (140)	261 (160)	258 (180)	253 (150)	
	CD <sup>f,g</sup>	269 (-140)		262 (-150)		255 (-110)	225 (-)
(R)-8b <sup>e</sup>	UV <sup>f</sup>	276 (330)		268 (370)		261 (280)	
	CD <sup>f,g</sup>	277 (-260)		270 (-300)		263 (-190)	225 (-)
(R)-11b <sup>e</sup>	UV <sup>f</sup>	289 (1500) <sup>h</sup>					238 (11 000)
	CD <sup>f</sup>	289 (-350) <sup>h</sup>					255 (-900)
$(\alpha R, \beta S)$ -12b	UV <sup>f</sup>	267 (83) <sup>i</sup>	264 (150)		257 (200)		
	CD <sup>f</sup>	268 (-850)		261 (-980)		255 (-660)	227 (+220)
$(\alpha R, \beta S)$ -13b	UV <sup>f</sup>	275 (200)		267 (260)		260 (230)	
	CD <sup>f</sup>	275 (+120)		268 (+90)		262 (+60)	235 (+140)
$(\alpha R, \beta S)$ -14b	UV	282 (1400) <sup>i</sup>		276 (1600)			226 (9500)
	CD	283 (+580) <sup>i</sup>		279 (+620)		229 (+5500)	220 ( $\pm 0$ )
$(\alpha R, \beta R)$ -15b <sup>e</sup>	UV <sup>f</sup>	267 (79) <sup>i</sup>	264 (150)		257 (190)		
	CD <sup>f</sup>	268 (+540)		261 (+610)		255 (+410)	225 ( $\pm 0$ )
$(\alpha R, \beta R)$ -16b	UV <sup>f</sup>	275 (210)		267 (290)		260 (250)	
	CD <sup>f</sup>	275 (-490)		268 (-500)		262 (-290)	236 (+150)
$(\alpha R, \beta R)$ -17b <sup>e</sup>	UV	282 (1100)		276 (1300)			226 (8400)
	CD	282 (-1100) <sup>i</sup>		277 (-1200)		223 (-5100)	218 (-4900)

<sup>a</sup> For previously unreported CD spectra,  $c$   $3.66 \times 10^{-3}$  to  $9.29 \times 10^{-2}$  g/100 mL, length 1 cm; temperature 25–28 °C. <sup>b</sup> Molar absorptivity. <sup>c</sup> Molecular ellipticity. <sup>d</sup> Additional UV and CD maxima were usually observed at shorter wavelength. No sign inversion of the maxima at shorter wavelength was observed in any CD spectrum. <sup>e</sup> Enantiomer used. <sup>f</sup> Hydrochloride examined in dilute methanolic potassium hydroxide. <sup>g</sup> Spectrum reported in ref 15. <sup>h</sup> Charge transfer band. <sup>i</sup> Shoulder.

absolute configurations of the para-substituted norephedrine (13, 14, 16, and 17) were established by application of the



salicylideneimino chirality rule<sup>20</sup> to an interpretation of the CD spectra of their *N*-salicylidene derivatives. The ultraviolet absorption (isotropic) (UV) and CD spectra of the respective free bases (5b, 8b, and 11b–17b) are also compared and analyzed. These spectra were usually obtained by measurement with solutions prepared from the respective hydrochlorides in dilute methanolic potassium hydroxide.

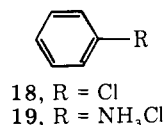
This analysis seemed useful in that while Sznatzke's rule is important in focusing attention on the possible role of the spectroscopic moment in relation to the chiroptical properties of the benzene chromophore, complete clarity is frustrated by the rule's inability to account for all experimental observations. Further, there are now in the literature other reports concerning the <sup>1</sup>L<sub>b</sub> Cotton effects displayed by a wide variety of benzenoid compounds which can be used to facilitate and to test our analysis.

## Results and Discussion

The UV and CD spectra of the  $\beta$ -phenylalkylamine hydrochlorides and  $\beta$ -phenylalkylamines are shown in Tables II and III. The data are tabulated for the enantiomers with the *R* configuration at the chiral center to which the nitrogen atom is attached, regardless of the configuration of the substance actually used.

As seen in the tables, the UV and CD spectra of a salt are not, except for (R)-11a, much different from those of its corresponding free base. For the  $\alpha$ -benzylethylamines (5, 8, 10, and 11) the sign of the <sup>1</sup>L<sub>b</sub> Cotton effects is unchanged on para substitution. For the chloro and ammonium compounds (8 and

11a), the molar absorptivity of the band origin ( $\epsilon_{0-0}$ ) is greater than that of their respective parents, 5 and chlorobenzene (18)



or aniline hydrochloride (19) (Table II). Thus the spectroscopic moments of the chloro, ammonium, and hydroxyl groups, the latter with a moment of the same sign as the chloro substituent,<sup>6,7</sup> are of the same sign as that of the chiral group, and para substitution then follows Sznatzke's rule.

On the other hand, para substitution of the norephedrine causes the sign of the <sup>1</sup>L<sub>b</sub> Cotton effects to be opposite from that of the unsubstituted parent (12–17), similar to that observed for (*S*)- $\alpha$ -phenylethylamine [(*S*)-9a] and some of its para-substituted derivatives [(*S*)-9b].<sup>16</sup> A change in configuration at the  $\alpha$ -carbon atom in the norephedrine compounds, however, does not alter the sign of their respective <sup>1</sup>L<sub>b</sub> Cotton effects.

The sign of the spectroscopic moment of the chiral substituent in the norephedrine derivatives (12–17) cannot be deduced unequivocally on the basis of the relevant UV data in Tables II and III. In view of similar observations with the para-substituted  $\alpha$ -phenylethylamines<sup>16</sup> (9), the sign reversal for para-substituted norephedrine, however, is not necessarily the result of the reversal in the resulting spectroscopic moment.

Inspection of the UV and CD spectral data in Tables II and III shows that for 12–17 the <sup>1</sup>L<sub>b</sub> Cotton effects arise by transitions to totally symmetric vibrational modes ( $a_1 \leftarrow a_1$ ) of the benzene chromophore and that sign alteration on para substitution is not the result of strengthened dichroic absorption associated with transitions to non-totally symmetric vibrational modes ( $b_2 \leftarrow a_1$ ).<sup>9,21,22</sup>

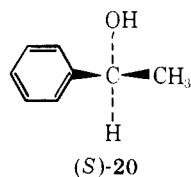
Manipulation of the data in Tables II and III gives an indication concerning the preferred conformation of the  $\alpha$ -benzylethylamines and norephedrine. Thus, algebraic addition of the dissymmetric factor of the <sup>1</sup>L<sub>b</sub> band origin ( $0 \leftarrow 0$  tran-

Table IV. Rotatory Contributions to the  ${}^1L_b$  Band Origins

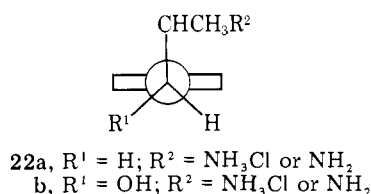
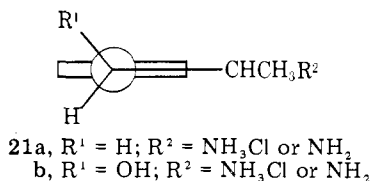
Compd	$[\theta]_{0-0}$	$(\Delta\epsilon_{0-0}^a/\epsilon_{0-0}) \times 10^3$	Contribution to $(\Delta\epsilon_{0-0}^a/\epsilon_{0-0}) \times 10^3$		
			$\beta S$	$\frac{\alpha R}{\text{Calcd}}$	Found <sup>b</sup>
Hydrochlorides					
( $\alpha R, \beta S$ )- <b>12a</b>	-720	-2.8	-2.0	-0.80	-0.79
( $\alpha R, \beta R$ )- <b>15a</b>	+280	+1.2			
( $\alpha R, \beta S$ )- <b>13a</b>	+150	+0.25	+0.38	-0.13	-0.20
( $\alpha R, \beta R$ )- <b>16a</b>	-300	-0.50			
( $\alpha R, \beta S$ )- <b>14a</b>	+500	+0.11	+0.15	-0.04	-0.07 <sup>c</sup>
( $\alpha R, \beta R$ )- <b>17a</b>	-700	-0.19			
Bases					
( $\alpha R, \beta S$ )- <b>12b</b>	-850	-3.1	-2.6	-0.50	-0.35
( $\alpha R, \beta R$ )- <b>15b</b>	+540	+2.1			
( $\alpha R, \beta S$ )- <b>13b</b>	+120	+0.18	+0.45	-0.27	-0.24
( $\alpha R, \beta R$ )- <b>16b</b>	-490	-0.71			
( $\alpha R, \beta S$ )- <b>14b</b>	+580	+0.13	+0.22	-0.09	<i>d</i>
( $\alpha R, \beta R$ )- <b>17b</b>	-1100	-0.30			

<sup>a</sup>  $\Delta\epsilon_{0-0} = [\theta]_{0-0}/3305$ . <sup>b</sup>  $\Delta\epsilon_{0-0}/\epsilon_{0-0}$  for the corresponding  $\alpha$ -benzylethylamine hydrochloride or free base. <sup>c</sup>  $l \leftarrow 0$  transition. <sup>d</sup> Not measured.

sition) ( $\Delta\epsilon_{0-0}/\epsilon_{0-0}$ ) for an ( $\alpha R, \beta S$ )-norephedrine to that of the corresponding  $\alpha R, \beta R$  isomer and division by two give a calculated contribution of the  $\alpha R$  chiral center; subtraction and division by two, the  $\beta S$  center contribution. Results of these calculations are given in Table IV. The excellent agreement between the  $\alpha R$  contributions and the experimentally observed values ( $\Delta\epsilon_{0-0}/\epsilon_{0-0}$  for the corresponding  $\alpha$ -benzylethylamine hydrochloride or free base), and between the calculated  $\beta S$  contribution of **12** and **15** and the experimentally observed dissymmetric factor ( $\Delta\epsilon_{0-0}/\epsilon_{0-0} = +2.2 \times 10^{-3}$ ) for (*S*)-1-phenylethanol<sup>21,23</sup> [(*S*)-**20**], the *S* configuration of **20**



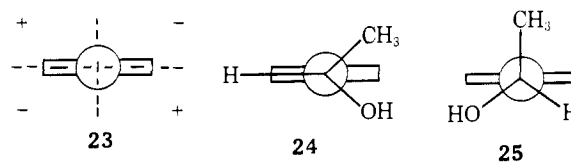
corresponding to the  $\beta R$  configuration in the norephedrine, suggests that there is little conformational alteration of the chiral carbon chain with respect to the phenyl group when a hydroxyl group is substituted for either of the benzylic hydrogens of an  $\alpha$ -benzylethylamine and that these two atoms are symmetrically situated with respect to the benzene ring plane. Two such conformers are possible; one with the  $C_\alpha$ - $C_\beta$  bond eclipsing (**21a**), the other with this bond orthogonal to the ring plane (**22a**). Molecular orbital calculations on ethylbenzene<sup>24</sup> indicate that conformer **22a** is preferred for **5**. Conformer **22b**, similar to those found by calculation for  $\alpha$ -



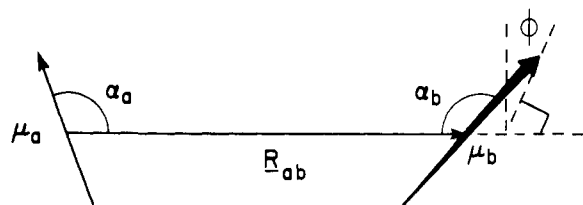
phenylethanol<sup>25</sup> (**20**) and mandelic acid<sup>14</sup> (**2**,  $R = H$ ), then is preferred for ( $\beta S$ )-**12** and ( $\beta S$ )-**15**, and conformational alteration on para substitution is small.<sup>14</sup>

As is also seen in Table IV, the sign reversal on para substitution of the norephedrine is due to the sign change in the  $\beta$  chiral center contribution. The latter can be subdivided into static (one-electron) as well as dynamic coupling (coupled oscillator) mechanisms.<sup>26</sup> The one-electron mechanism depends on the charge distribution of the asymmetric substituents while the dynamic coupling mechanism depends on the relative energies and orientations of the transition moments of the chromophore and of the substituents at the  $\beta$  chiral center. The dynamic coupling mechanism can further be classified as electric dipole-dipole coupling and magnetic-electric dipole-dipole coupling, the latter usually making a smaller contribution because of the higher moments involved. The sign reversal of the  ${}^1L_b$  Cotton effects on para substitution of the norephedrine can thus be interpreted in terms of the relative dominance of the one-electron mechanism making a particular contribution to the  $\beta$  center rotational contribution vs. the dynamic coupling mechanism making an additional contribution. In the unsubstituted ( $\beta S$ )-norephedrine [( $\alpha R, \beta S$ )-**12** and [( $\alpha S, \beta S$ )-**15**], the electric transition moment of the  ${}^1L_b$  band is quite small as evidenced from the molar absorptivities ( $\epsilon$ ). Consequently, the one-electron mechanism is dominant for the  $\beta$  chiral center and negative Cotton effects are observed. Upon para substitution, however, the transition moment becomes larger resulting in a positive contribution of the coupled oscillator mechanism overshadowing the one-electron contribution. This interpretation seems plausible since the coupled oscillator contribution depends on the transition moment to the second power while the one-electron contribution, roughly to the first power.

According to group theoretical considerations, for a chromophore with  $C_{2v}$  symmetry, a quadrant sector rule may be appropriate for the one-electron contribution.<sup>27</sup> Perturbation by a hydroxyl group for the  ${}^1L_b$  sector signs of an unsubstituted norephedrine is assigned as shown in **23**. This assignment is



based on calculation with (*S*)-1-phenylethanol [(*S*)-**20**] by Cervinka, Kral, and Malon<sup>25</sup> in which the hydrogen atom at the chiral center was taken as eclipsing the phenyl ring plane (**24**). The one-electron contribution due to the hydroxyl group lying in the lower right sector was calculated to be positive



**Figure 1.** Sense of a right-handed screw is shown for the transition moments separated by a distance  $R_{ab}$ .  $\mathbf{R}_{ab} = \mathbf{R}_b - \mathbf{R}_a$  is a vector directing from  $a$  to  $b$ .  $\phi$  is the dihedral angle and  $\alpha_a$  and  $\alpha_b$  are angles made by  $\mu_a$  and  $\mu_b$  with  $R_{ab}$ .

( $+2.2 \times 10^{-41}$  cgs units). Consequently in an unsubstituted ( $\beta S$ )-norephedrine [( $\alpha R, \beta S$ )-**12**] and [( $\alpha S, \beta S$ )-**15**], the hydroxyl group should make a negative contribution due to the one-electron mechanism with its magnitude similar to that calculated for (*S*)-**20** since conformer **22b** and that used by Cervinka<sup>25</sup> (**24**) place the hydroxyl group in the similar location of oppositely signed sectors.

The rotational strength,  $\mathbf{R}$ , due to the coupled oscillator mechanism can be calculated by<sup>28</sup>

$$\mathbf{R}_a = \sum_{a \neq b} \frac{2\pi \nu_a \nu_b \mu_a^2 \mu_b^2}{hc (\nu_b^2 - \nu_a^2)} GF \quad (1)$$

where

$$GF = \left[ \mathbf{e}_a \cdot \mathbf{e}_b - 3 \frac{(\mathbf{e}_a \cdot \mathbf{R}_{ab})(\mathbf{e}_b \cdot \mathbf{R}_{ab})}{R_{ab}^2} \right] \frac{\mathbf{e}_a \times \mathbf{e}_b \cdot \mathbf{R}_{ab}}{R_{ab}^3} \quad (2)$$

and  $\mathbf{e}_a$ ,  $\mu_a$ , and  $\nu_a$  are the direction, magnitude, and frequency of the chromophore transition moments and  $\mathbf{e}_b$ ,  $\mu_b$ , and  $\nu_b$  are the analogous quantities for the transition in the adjacent group.  $R_{ab}$  in eq 2 is the distance between the two groups, directed from the chromophore,  $a$ , to the vicinal group,  $b$  (Figure 1). The  $GF$  quantity can further be expressed in terms of  $\alpha_a$  and  $\alpha_b$ , angles made by  $\mathbf{e}_a$  and  $\mathbf{e}_b$  and  $R_{ab}$ , and  $\phi$ , the dihedral angle (Figure 1) as<sup>29</sup>

$$GF = [2 \cos \alpha_a \cos \alpha_b + \sin \alpha_a \sin \alpha_b \cos \phi] \times \frac{\sin \alpha_a \sin \alpha_b \sin \phi}{R_{ab}^2} \quad (3)$$

The sign of the coupled oscillator contribution to the rotational strength can be calculated by measuring the angles  $\alpha_a$ ,  $\alpha_b$ , and  $\phi$ . In fact, for an asymmetric carbon atom directly attached to the benzene ring, the coupled oscillator contribution to the  ${}^1L_b$  Cotton effects from bonds attached directly to this carbon atom can be shown and verified by numerical calculation<sup>29</sup> to obey a quadrant rule with sector signs exactly opposite to the one-electron contribution of the hydroxyl group shown in **23**. Thus with conformer **22b**, the  $C_\alpha$ - $C_\beta$  bond makes no contribution since it lies on a sector plane while the C-O bond makes a positive contribution and that of the C-H bond is negligible.<sup>28</sup> Substituting appropriate angles for conformation **25** and relevant values for the other quantities<sup>28</sup> into eq 1 and 3, a rotational strength of  $+7.5 \times 10^{-42}$  cgs units was calculated for (*R*)-**20** using  $\mu_a = 0.55 \times 10^{-18}$  cm esu for the  ${}^1L_b$  transition moment, the *R* configuration of **20** being the same as the  $\beta S$  configuration in the norephedrine (**22b**). In this calculation the transition moment was located at the center of the chromophore and directed perpendicular to the benzene  $C_2$  axis while the transition moment magnitude was found by CNDO/S calculation<sup>30</sup> on toluene. An alternate calculation performed with the transition moment distributed along the benzene carbon-carbon bonds<sup>28</sup> also results in a positively signed coupled oscillator contribution to the rotational strength.

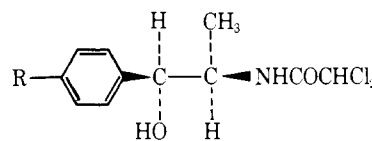
It is to be noted that Cervinka<sup>25</sup> calculated the rotational

strength contribution of the coupled oscillator mechanism for (*S*)-**20** to be  $+7.13 \times 10^{-42}$  cgs units. That both calculations give positive contributions stems from the choice of preferred conformation, **24** vs. **25**. Other calculations by Cervinka<sup>25</sup> give the minimum nonbonded interactions in (*S*)-**20** when the methine hydrogen atom-benzene ring plane dihedral angle is  $\sim +15^\circ$ , and in the rotational strength calculation this angle was taken as zero (**24**). In our calculation with (*R*)-**20**, the angle is taken as  $-30^\circ$  (**25**), an angle similar to that calculated for (*S*)-mandelic acid.<sup>14</sup>

It should be noted, however, that a direct rotational strength calculation using the CNDO/S method has been performed for (*S*)-**20** in several conformations by Dickerson and Richardson.<sup>31</sup> Negative rotational strengths for the  ${}^1L_b$  transition, opposite to the experimental observation with (*S*)-**20**, were calculated for the conformer **24** considered by Cervinka, Kral, and Malon<sup>25</sup> and for the enantiomer of conformer **25**.

Our present calculations and experimental observations, however, support our contention that in the unsubstituted ( $\beta S$ )-norephedrine the  $\beta$  chiral center determines the sign of the  ${}^1L_b$  Cotton effects with the one-electron mechanism (negative contribution) dominating over the coupled oscillator mechanism (positive contribution). The sign reversal on para substitution occurs since an increase in the transition moment results in an increase in the positive coupled oscillator contribution which then becomes dominant.

Similar considerations of the dominant contribution to the  ${}^1L_b$  Cotton effects may also be applied to explain the sign changes on para substitution of other related compounds: mandelic acid<sup>11,14</sup> (**2**,  $R = H$ ),  $\beta$ -hydroxy- $\beta$ -phenylpropionic acid<sup>12</sup> (**3**,  $R = H$ ), and *N*-(dichloroacetyl)norephedrine<sup>32,33</sup> (**26**,  $R = H$ ).



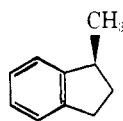
**26**,  $R = H, Br, \text{ or } I$

The possibility of dominance of the coupled oscillator mechanism as an explanation for the sign reversal on para substitution of the (*S*)- $\alpha$ -phenylethylamines [(*S*)-**9a**] was considered by Gottarelli and Samori.<sup>16</sup> This was abandoned because of their inability to interpret the observed  ${}^1L_b$  Cotton effects for (*S*)- $\alpha$ -(*p*-cyanophenyl)ethylamine [(*S*)-**9c**]. The cyano group with a large spectroscopic moment opposite in sign to that of the chiral substituent should reverse the sign of the overall transition moment of the benzene chromophore resulting in both the one-electron and coupled oscillator mechanism making negative contributions to the rotational strength in contrast to the observed positive  ${}^1L_b$  Cotton effects. This difficulty may be resolved if one considers the possibility of vibronic dominance of the  ${}^1L_b$  band in this compound. This is not unreasonable since the  ${}^1L_a$  absorption maximum has been bathochromically shifted from 214 nm in  $\alpha$ -phenylethylamine to 233 nm (238 nm in the CD spectrum) for the *p*-cyano derivative. According to vibronic theory<sup>34,35</sup> a transition can borrow rotational strength from a neighboring transition through molecular vibration with the intensity inversely proportional to the square of the frequency difference and directly proportional to the sign and intensity of the donor rotational strength. A rough calculation indicates an intensity enhancement factor of 2-5 for the dichroic absorption associated with transitions to non-totally symmetric vibrational modes for (*S*)-**9c** which may dominate the circular dichroism associated with the  ${}^1L_b$  band. An alternate explanation could be that the presence of the cyano group on the benzene chromophore results in low-lying  $\sigma$ - $\pi^*$  transitions<sup>36</sup> which may mix with the

$^1L_b$  transition by dissymmetric perturbation to produce a strong positive one-electron contribution. The positive sign for the  $^1L_b$  CD band for (*S*)-**9c**, the same as that of (*S*)-**9a** but opposite to that for the other para-substituted analogues [(*S*)-**9b**] with the same absolute configuration, may be a manifestation of these  $\sigma-\pi^*$  transitions.

The observation that para substitution of a (*R*)- $\alpha$ -benzylethylamine [(*R*)-**5a**] and its salt [(*R*)-**5b**], L-phenylalanine (**1a**), and  $\alpha$ -phenoxypropionic acid (**4**, R = H) does not reverse the sign of the  $^1L_b$  Cotton effects may be due to both the one-electron and the coupled oscillator mechanisms making contributions of the same sign or the latter mechanism already dominating in the unsubstituted parent compound.

Our analysis clearly indicates that no single universally applicable sector rule can be devised for prediction of the sign of the  $^1L_b$  Cotton effects of the benzene chromophore since the one-electron and the coupled oscillator mechanisms by which the observed Cotton effects are generated make rotatory contributions of approximately equal magnitude. This analysis of the CD spectra of the benzene chromophore in terms of the interplay of the one-electron and coupled oscillator mechanisms is similar to that presented by Cervinka, Kral, and Malon<sup>25</sup> and that utilized by Allen and Schnepf<sup>37</sup> for (*S*)-1-methylindan [(*S*)-**26**].



(S)-26

It appears that for open-chain chiral substituents on the benzene chromophore with  $\epsilon < 100$  for the  $^1L_b$  transition, the one-electron mechanism is dominant in the determining of the sign of associated Cotton effects. With  $\epsilon > 200$ , the coupled oscillator mechanism may be the more important.

## Experimental Section

Isotropic ultraviolet absorption (UV) spectra were measured using a Cary Model 14 spectrometer with the normal variable slit. Circular dichroism (CD) spectra were measured with a Cary Model 60 spectropolarimeter equipped with a CD Model 6001 accessory. The slit was programmed for a spectral bandwidth of 1.5 nm. All spectra were determined in methanol at 25–28 °C and, except for ( $\alpha R, \beta S$ )-**14b** and ( $\alpha S, \beta S$ )-**17b**, the spectra of the free bases were obtained by measurement with solutions prepared from the respective hydrochlorides in dilute methanolic potassium hydroxide.

(*R*)- $\alpha$ -(*p*-Hydroxybenzyl)ethylamine hydrochloride [(*R*)-**10a**] had mp 176–179 °C (sealed capillary, corrected) and  $[\alpha]^{25}_D -26^\circ$  (*c* 2.01,

H<sub>2</sub>O, 1 dm) [lit.<sup>38</sup>  $[\alpha]^{17}_D -52.0^\circ$  (C<sub>2</sub>H<sub>5</sub>OH) for the free base] and was a gift from Smith, Kline & French Laboratories.

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