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The Salicylidenamino[1] Chirality Rule: A Method for the Establishment of the Absolute Configurations of Chiral Primary Amines by Circular Dichroism

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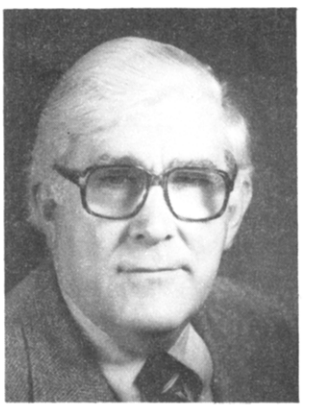

Howard Smith is a Professor of Chemistry at Vanderbilt University where he joined the faculty in 1959. He was born and grew up in San Francisco, CA. After receiving his B.S. degree (1951) from the University of California at Berkeley and his M.S. degree (1954) and Ph.D. degree (1957) from Stanford University for work with Richard H. Eastman, Professor Smith had postdoctoral training as a National Institutes of Health Fellow at Wayne State University, Detroit, MI, with Carl Djerassi and at the Swiss Federal Institute of Technology, Zurich, with Vladimir Prelog. Professor Smith's major research interests are concerned with stereochemistry and the interaction of chiral molecules, natural and synthetic, with biological receptor systems.

I. Introduction

A. Scope

Some years ago,[2] we reported the possible use of Schiff base derivatives of salicylaldehyde (**1a**) and 5-bromosalicylaldehyde (**1b**) and chiral primary amines for the establishment of stereochemical features of the chiral amines. The study of such derivatives was based on the method of chromophoric derivatives,[3,4] by which

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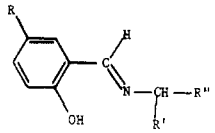


1a, R = H
b, R = Br

a chiral compound, such as an amine, alcohol, or alkene, having no electron absorption (EA) band in an easily accessible spectral range,[5] is converted to a derivative with absorption in either the visible or quartz ultraviolet region. Since this new chromophore is situated in a chiral environment, it is to be anticipated that the derivative would display an optical rotatory dispersion (ORD) curve[6] and circular dichroism (CD) spectrum[7] with a Cotton effect (CE)[6,7] associated with each of its EA bands. The sign and magnitude of the observed CEs should give information concerning the stereochemical environment of the chromophore, much the same as the ORD curve and CD spectrum of a chiral ketone give information concerning the steric disposition of substituents in the vicinity of the carbonyl chromophore.[8]

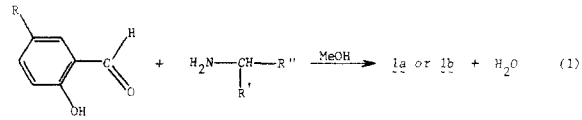
Our early work[9-16] with the *N*-salicylidene derivatives of chiral primary amines indicated that the CEs associated with their strong EA bands in the quartz ultraviolet region could be used as an empirical correlation device for the establishment of the absolute configurations of the amines. During this period, others[17-27] also used such derivatives in a similar way.

Subsequently we showed[28] that the coupled oscillator mechanism of Kuhn and Kirkwood[29] accounts for the observed CEs. The method for the prediction of the sign of these CEs was formulated as the salicylideneamino[1] (SA) chirality rule and was successfully applied to the interpretation of the CD spectra of a great number of *N*-salicylidene derivatives of chiral primary amines, including those of α- and β-arylalkylamines,[28,30] 1-alkyl-2-propynylamines and 1-alkyl-2-propenylamines,[31] and aliphatic and alicyclic amines,[32] including terpene[33] and steroidal amines,[34] α-amino acids and esters,[35] and amino sugars.[36] In connection with other work, we[37-41] and others[42] have confirmed or established the absolute configurations of various other chiral primary amines by application of this rule.

We now wish to review our work and to outline the general application of the SA chirality rule. The EA, ORD, and CD of azomethines, including those of Schiff bases derived from salicylaldehyde, were surveyed earlier by Bonnett.[43] Not included was any discussion of the SA chirality rule.

B. Formation of *N*-Salicylidene Derivatives

For spectral measurements the *N*-salicylidene (**1a**) or *N*-5-bromosalicylidene derivatives (**1b**) are prepared by warming a slight excess of salicylaldehyde (**2a**) or 5-bromosalicylaldehyde (**2b**) with the amine in methanol (reaction 1).[9] The reaction is complete in 15 min, and

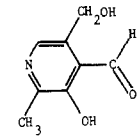


(1)

2a, R = H
b, R = Br

in most cases the yield is nearly quantitative. The derivative may be isolated or used in situ.[9,10] An advantage is gained with the *N*-5-bromosalicylidene derivatives in that they, with spectral properties essentially the same as the *N*-salicylidene derivatives,[9,16,28,30] are more apt to be solids at room temperature and are thus more easily isolated and purified.

In a similar reaction of pyridoxal (**3**) with an amine, the Schiff base is also formed.[44] If the amine moiety



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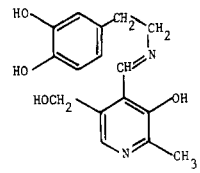

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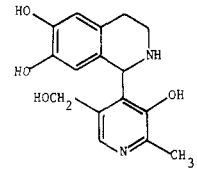
contains a nucleophile, the azomethine carbon atom of the Schiff base may act as an electrophile and an intramolecular cyclization product may be formed.[44-47] Thus the Schiff base (**4**) of **3** with β-(3,4-dihydroxyphenyl)ethylamine yields the tetrahydroisoquinoline **5**,



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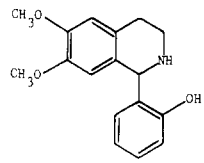
the hydroxyl group para to the position of ring closure facilitating the ring closure reaction.[48] Ring closure products (**6** and L-**7**) of salicylaldehyde (**1a**) with β-



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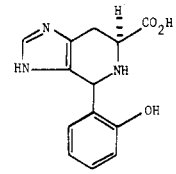
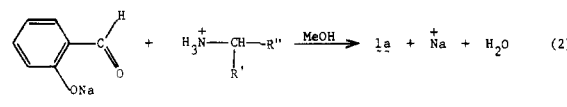


L-7

(3,4-dimethoxyphenyl)ethylamine and L-histidine have been reported[47,49] and have spectral properties different from those of the Schiff bases.[47] Similar derivatives of the salicylaldehyde Schiff bases are less readily formed than those of the pyridoxal analogues[47] and are not obtained under the conditions used for the formation of the *N*-salicylidene Schiff bases.

In general, the *N*-salicylidene derivatives of primary amines are chemically and optically stable as solids or liquids or as solutions at room temperature.[10] Those of α-amino esters are racemized or epimerized at the α carbon atom when distilled.[10] This optical instability is dependent on the presence of two electron-withdrawing groups at the chiral center, and *N*-salicylidene derivatives not possessing this structural feature are chemically and optically stable during distillation at moderate temperatures or during recrystallization.

N-Salicylidene derivatives (**1a**) can also be formed by mixing sodium salicylaldehyde (**8**) with an amine salt in methanol (reaction 2).[35] Since **8** and the amine salt



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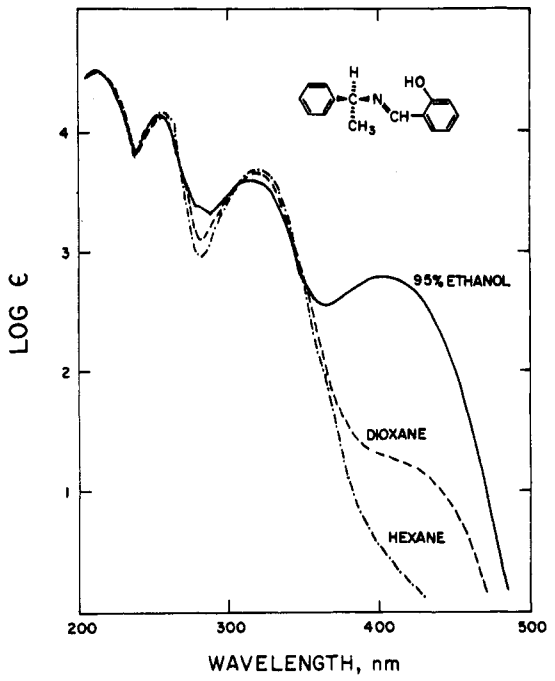


Figure 1. Electronic absorption (EA) spectrum of the *N*-salicylidene derivative of (*S*)-α-phenylethylamine [(*S*)-**13a**] in various solvents.

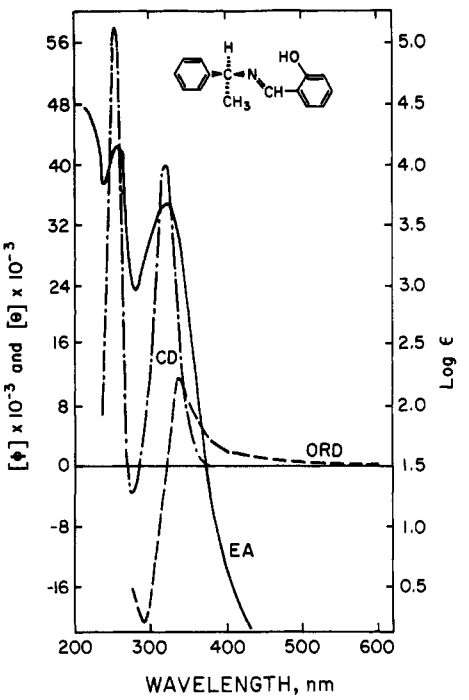


Figure 2. Electronic absorption (EA) spectrum and optical rotatory dispersion (ORD) curve in hexane and circular dichroism (CD) spectrum in isooctane of the *N*-salicylidene derivative of (*S*)-α-phenylethylamine [(*S*)-**13a**].

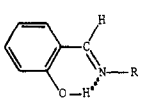
are usually solids at room temperature, 1 or 2 mg of **8** and the salt are easily weighed before mixing. By use of the in situ procedure, the CD spectra of α-amino acid and ester derivatives can also be measured.[35] With an α-amino acid, a methanolic solution of the Schiff base of the sodium salt of the α-amino acid (**1a**, R″ = CO_2^-) is obtained.

It is to be noted, however, that when the CD spectrum of an *N*-salicylidene derivative formed in situ is compared with that of the isolated derivative, the CD maxima of the former are usually less intense than those of the latter due to incomplete formation of the derivative in situ.[35] Polarimetric studies[35] of the rate of formation of the derivatives indicate the equilibrium is achieved at room temperature within 2 h and that the derivatives, including those of the α-amino esters, are optically stable for at least 12 h even when a large excess of **8** is used.

II. Salicylidenamino Chromophore

A. Electronic Absorption Spectra

The isotropic electronic absorption (EA) spectra of the *N*-salicylidene derivatives (**1a**) of primary amines in nonpolar solvents (hexane and isooctane) (Figure 1) exhibit characteristic absorption bands at about 315 (log ϵ_{max} 3.7), 255 (4.1–4.2), and 215 nm (4.4–4.5),[33] designated as bands I, II, and III, respectively,[28] and assigned to $\pi \rightarrow \pi^*$ transitions of the intramolecularly hydrogen-bonded salicylidenamino (SA) chromophore (**9**).[50]



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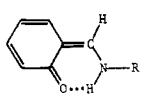

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In polar solvents, a broad band at about 400 nm (log ϵ_{max} 1.3–1.9 in dioxane[25] and 3.1–3.4 in methanol[33] and ethanol[25]) and a shoulder near 280 nm (log ϵ_{max} 3.5–3.7 in ethanol[25]) become evident, and the three other bands show a slight decrease in intensity (Figure 1).[25,33] Earlier these two additional bands were suggested as being due to solvated forms of the derivative,[51,52] but it is now generally concluded that they result from a quinoid form (**10**) of the derivative,[43,50,53] stabilized by and in relatively greater amount in polar solvents.

The EA spectra of the *N*-5-bromosalicylidene derivatives (**1b**) are essentially the same as those of **1a** except that the longest wavelength bands of the former are at about 415 and 328 nm.[9]

B. Optical Rotatory Dispersion Curves and Circular Dichroism Spectra

The *N*-salicylidene and *N*-5-bromosalicylidene derivatives of chiral primary amines show ORD curves[9,10] and CD spectra[11] with CEs associated with bands I and II[28] and in polar solvents with the band near 400 nm[9-11] (Figures 2 and 3). The CE associated with band III is difficult to measure and is frequently not observed. In some spectra, there is an additional, comparatively weak CD maximum between bands I and II and centered at about 273 nm (Figures 2 and 3). Sometimes this CE has been attributed to the quinoid form,[33,35] but when it occurs in nonpolar solvents, it cannot be thus assigned. On the basis of spectral observations with various Schiff bases[54] and CNDO/S calculations on the azomethine and conjugated azomethine chromophores,[55] the 275-nm CE is assigned to an $n \rightarrow \pi^*$ transition of the SA chromophore. For some *N*-salicylidene derivatives containing an unsaturated group in the amine moiety, the 275-nm CD maximum may also be due to a transition at about this same wavelength for the unsaturated group.[54]

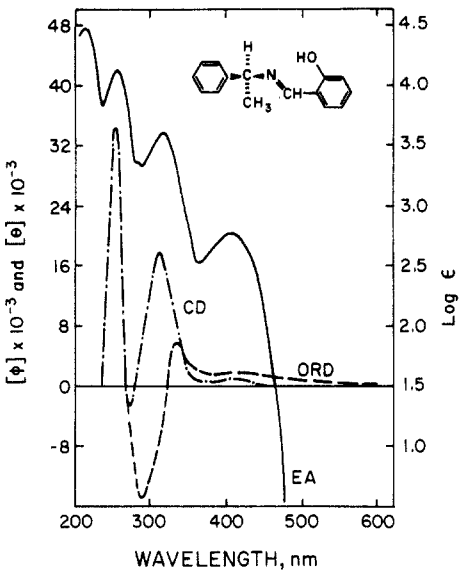


Figure 3. Electronic absorption (EA) spectrum and optical rotatory dispersion (ORD) curve in 95% ethanol and circular dichroism (CD) spectrum in absolute ethanol of the *N*-salicylidene derivative of (*S*)-α-phenylethylamine [(*S*)-**13a**].

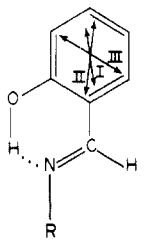


Figure 4. Approximate electric transition moment directions for bands I, II, and III of the salicylidenamino (SA) chromophore.

C. Generation of Cotton Effects and the Salicylidenamino Chirality Rule

Three important mechanisms that account for the generation of CEs are well-known:[29] (1) the one-electron mechanism of Condon, Altar, and Eyring; (2) the coupled oscillator model of Kuhn and Kirkwood; and (3) the coupling of a magnetic moment of one group with the electric moment of another. The magnitude of the CEs and the general features of the CD spectra of *N*-salicylidene derivatives (Figures 2 and 3) indicate that the dominant mechanism for generation of the CEs is electric dipole–dipole coupling (mechanism 2). By

(*R*)-**11** (*R*)-**12**

use of the exciton splitting in the CD spectra of the *N*,*N*′-di-5-bromosalicylidene derivatives of (*R*)-*trans*-1,2-cyclohexanediamine [(*R*)-**11**] and (*R*)-1,2-propanediamine[28] [(*R*)-**12**] and CNDO/S calculations,[55] the electric transition moment directions for the SA chromophore were determined (Figure 4). The CEs associated with the transitions near 315 (band I) and 255 nm (band II) are the result of coupling of these electric transition moments with electric transition moments in the amine moiety and lead to a statement of the SA chirality rule: when the coupled electric transition moments are arbitrarily assigned as being directed away from each other (Figure 5) in order to make the dipole

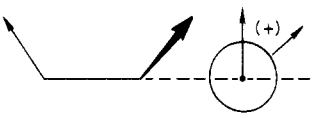


Figure 5. Sense of a right-handed screw for coupled oscillators leading to a positive contribution to the circular dichroism of bands I and II of the salicylidenamino (SA) chromophore.

interaction energy positive and when the transition of a coupling group in the amine moiety is at a shorter wavelength than bands I and II, positive chirality (right-handed screw) results in a positive contribution to the CEs of bands I and II and negative chirality (left-handed screw) results in a negative contribution to the CEs. The sign of the observed CEs is the algebraic sum of these contributions, the sum being related to the distribution of groups in the amino moiety with respect to the SA chromophore. Simple conformational analysis can then be used to predict the sign of the observed CEs for a particular enantiomer.

III. Applications to Amines with Unsaturated Groups

A. General Considerations

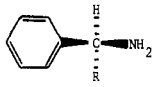
For the *N*-salicylidene derivatives of amines having unsaturated groups geminal or vicinal to the amino group, the CEs for bands I and II are related to the chirality that the transition moments of the SA chromophore have with the effective $\pi \rightarrow \pi^*$ transition moments of the unsaturated groups. Straightforward applications have been demonstrated with amines containing unsubstituted and substituted aromatic groups, carboxylate groups, and carbon–carbon double and triple bonds. When one such group is present, the CEs of bands I and II are strong and have the same sign. Cancellation may occur when two or more such groups occur, but frequently the CD spectra are useful for configurational assignments.

B. One Unsaturated Group Geminal to the Amino Group

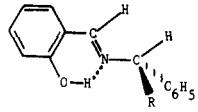
1. α-Phenylalkylamines

For the *N*-salicylidene derivatives of α-phenylalkylamines, the CEs associated with bands I and II arise by coupling of the electric transition moments of these transitions with the ^1L_a and ^1B_a electric transition moments of the benzene ring that lie below 220 nm[28] and that are aligned along the benzene ring attachment bond. The ^1B_b transition moment is perpendicular to the phenyl group attachment bond, and the coupling of this transition moment, as well as that of the ^1L_b transition moment, will be averaged out due to the phenyl group rotation about its attachment bond.

The algebraic sum of the chirality of the effective couplings of the transition moments is deduced by conformational analysis. Thus, the three conformers of lowest energy for the *N*-salicylidene derivative of (*S*)-α-phenylethylamine [(*S*)-**13a**] are depicted as **14a**–**c**[13] (R = CH_3), each conformer having a particular chirality of coupling as shown. Conformer **14a** makes a positive contribution to the CEs of bands I and II (Figure 6) while **14b** makes a negligible contribution due to the near coplanarity of the respective transition



(*S*)-**13a**, R = CH_3
b, R = CH_3CH_2
c, R = $C(CH_3)_3$
d, R = $CH_2CO_2CH_2CH_3$
(*R*)-**13e**, R = CH_2OH



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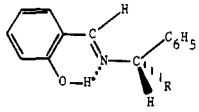
14a



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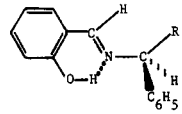
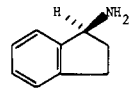
14b



(−)
14c

moments. The contribution of **14c** is negative but less than that of **14a** because the latter is more stable. Thus the *N*-salicylidene derivative of (*S*)-**13a** displays strong positive CEs near 255 and 315 nm (Figures 2 and 3 and Table I).[11,28,35] In methanol, the 397-nm CE, not observed when isooctane is the solvent, is due to the quinoid form (**10**) and that at 275 nm, persisting in isooctane, is due to the n → π* transition of the azomethine group.[54]

Changes in the effective bulk size of the alkyl group, R group in **14a–c**, have only a minimal effect on the conformational equilibrium of an *N*-salicylidene derivative of a chiral α-phenylalkylamine, and conformer **14a** makes the most important contribution to the CD spectrum. Thus, the *N*-salicylidene derivatives of (*S*)-**13b–d** and (*R*)-**13e** display CD spectra very similar to that of the *N*-salicylidene derivative of (*S*)-**13a** with positive CEs for bands I and II.[11,28,41,56] The absolute configurations of (*S*)-**13b,c** were originally assigned on the basis of the ORD of their *N*-salicylidene derivatives.[10] These assignments were each confirmed by subsequent chemical degradation.[57,58]



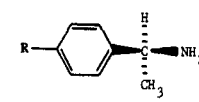
(*S*)-**15**

For (*S*)-1-aminoindan [(*S*)-**15**], the observed[13] positive CEs are also predicted by a similar analysis.

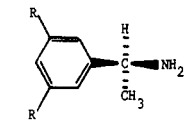
2. Ring-Substituted α-Phenylalkylamines

Substitution at various positions on the benzene ring of a chiral α-phenylalkylamine should have little effect on the CEs of bands I and II of its *N*-salicylidene derivative, except for possible minor variations in intensity reflecting changes in the magnitude of the effective transition moments along the phenyl group attachment bond, since it is only the component of the π → π* electric transition moments along the phenyl group attachment bond that strongly couple with the transition moments of bands I and II of the SA chromophore.[28]

Thus, the CD spectra of the *N*-salicylidene derivatives of the para-substituted (*S*)-α-phenylethylamines [(*S*)-**16a–c**] show strong positive CEs for bands I and II,[40] the configurational assignments for (*S*)-**16a–c** having been made earlier on the basis of the CD spectrum of the respective *N*-phthaloyl derivatives.[59] The



(*S*)-**16a**, R = CH_3
b, R = Cl
c, R = Br
d, R = CF_3

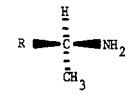


(*S*)-**17a**, R = CH_3
b, R = Cl

N-salicylidene derivatives of the enantiomer of **16d** and **17a,b** showing positive CEs for bands I and II were assigned the *S* configuration using the SA chirality rule.[40]

3. Other α-Arylalkylamines

The SA chirality rule may be generalized to include other α-arylalkylamines since for generation of the CEs of bands I and II, the effective components of π → π* transitions of the aryl groups are along their attachment bonds. The conformational equilibrium for these derivatives is similar to that for *N*-salicylidene-α-phenylethylamine (**14a–c**), and the observed positive CEs for bands I and II in the spectra of the *N*-salicylidene derivatives of (*S*)-α-(2-pyridyl)ethylamine[15] [(*S*)-**18a**] (Table I) and (*S*)-**18b–e**[10,15,35,38] are in agreement with this generalization of the SA chirality rule. Amines (*S*)-**18a–d** were of previously established configuration[15,35,38] while the *S* configuration was assigned to the enantiomer of **18e** that showed positive CEs for bands I and II for its *N*-salicylidene derivative.[10] The strong negative CE at 285 nm in the CD spectrum of the (*S*)-α-(1-naphthyl)ethylamine [(*S*)-**18e**] derivative (Table I) is due to the ^1L_a transition of the naphthyl group. The *S* configuration assigned to the particular enantiomer of **18e** used to prepare this *N*-salicylidene derivative was subsequently confirmed by chemical correlation.[60]

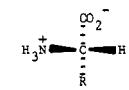


(*S*)-**18a**, R = 2-pyridyl
b, R = 4-pyridyl
c, R = 2-thienyl
d, R = 2-furanyl
e, R = 1-naphthyl

4. Aliphatic α-Amino Acids

Since a protonated primary amino group does not react with salicylaldehyde, the *N*-salicylidene derivative of an α-amino acid is more conveniently formed in situ by treating the acid with sodium salicylaldehyde (**8**) (section IB). The product in this reaction is the sodium salt of the *N*-salicylidene derivative of the α-amino acid (**1a**, R″ = CO_2^-).

The CD spectrum of the *N*-salicylidene derivative of L-alanine (L-**19a**) is the same as those of other aliphatic



L-**19a**, R = CH_3
b, R = CH_3CH_2
c, R = $(CH_3)_2CH$
d, R = $(CH_3)_2CHCH_2$
e, R = $CH_3CH_2C(CH_3)H$
f, R = *allo*-$CH_3CH_2C(CH_3)H$
g, R = *c*-C_6H_{11}
L-**19h**, R = *c*-$C_6H_{11}CH_2$
i, R = $HOCH_2$
j, R = $CH_3C(OH)H$
k, R = CH_3SCH_2
l, R = $CH_3SCH_2CH_2$
m, R = $HSCH_2$

TABLE I. Circular Dichroism Data for the *N*-Salicylidene Derivatives of Some Chiral Amines with One Unsaturated Group Geminal or Vicinal to the Amino Group

	R—C(H)—SA, R′		CD max,[a] λ, nm ([θ][b])					
amine	R	R′	quinoid	band I	other	band II	band III	ref
(*S*)-**13a**	C_6H_5	CH_3	397 (+1700)	316 (+16 000)	275 (−2300)[c]	252 (+33 000)	222 (−41 000)	28
(*S*)-**18a**[d]	2-C_5H_4N	CH_3		312 (+57 000)		262 (+93 000)		15
(*S*)-**18e**[e]	1-$C_{10}H_7$	CH_3	406 (+1400)	316 (+26 000)	285 (−18 000)[f]	256 (+57 000)		11
L-**19a**[d]	CO_2^-	CH_3	402 (+3600)	314 (+6400)	273 (−5000)[c]	252 (+5100)	229 (−16 000)	35
L-**19k**[d]	CO_2^-	CH_3-SCH$_2$		317 (−2500)		264 (−15 000) 246 (+4600)	228 (−12 000)	35
L-**23a**[d]	CO_2CH_3	CH_3		315 (+1900)		262 (−3600)	229 (−7600)	35
(*S*)-**24a**[g]	CH≡C	CH_3	400 (+120)[h]	316 (+4900)	269 (−6100)[c]	251 (+5900)	219 (−7800)	31
(*S*)-**25a**[g]	CH_2=CH	CH_3	400 (+790)	316 (+6000)	271 (−3500)[c]	251 (+15 000)	210 (+9400)	31
(*S*)-**28a**[e]	$C_6H_5CH_2$	CH_3	399 (+2000)	312 (+15 000)		251 (+39 000)		11
(*S*)-**31d**[e,i]	*p*-$O_2NC_6H_4CH_2$	CH_3	415 (+1200)	327 (+23 000)	291 (−3000)[j]	266 (+25 000) 252 (−21 000)		28

[a] Methanol as the solvent or as otherwise noted. [b] Molecular ellipticity. [c] Assigned to the n → π* transition of the azomethine group. [d] Derivative formed in situ. [e] Absolute ethanol as the solvent for this spectrum. [f] Assigned to the ^1L_a transition of the naphthalene group. [g] Enantiomer used. [h] Shoulder. [i] *N*-5-Bromosalicylidene derivative. [j] Assigned to the ^1L_b transition of the phenyl group of the amine moiety.

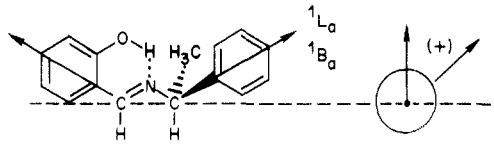


Figure 6. Chirality of the coupled electric transition moments in the preferred conformer (**14a**) for the *N*-salicylidene derivative of (*S*)-α-phenylethylamine [(*S*)-**13a**].

α-amino acid derivatives[35,42] (L-**19b–h**). In the CD spectrum of the derivative of L-**19a** (Figure 7 and Table I), the negative maximum at 273 nm and the positive one at 402 nm were originally assigned to the quinoid form[35] (**10**), but subsequently that at 273 nm was reassigned[54] to an n → π* transition of the azomethine group strongly coupled to electronically allowed π → π* transitions below 210 nm of the carboxylate group.[61] The 273-nm maximum may also be related to a very weak transition (molar absorptivity ≃ 10^{-2}) in the vicinity of 275 nm in the EA spectrum of aliphatic carboxylic acids and esters.[62] This band for the carboxyl group may also explain the strong CE appearing near 322 nm in the CD spectrum of 2-methoxy-2,4-diphenyl-3(2*H*)-furanone (MDPF) and 4-phenylspiro[furan-2(3*H*)-1′-phthalan]-3,3′-dione (fluorescamine) derivatives of chiral α-amino acids.[63]

For the *N*-salicylidene derivatives, the maxima near 314, 252, and 229 nm are identified as CD bands I, II, and III, respectively, and arise by transition moment dipole–dipole coupling of the carboxylate group with the SA chromophore.

The longest wavelength absorption band of the carboxylate group occurs at about 210 nm, and its identity as an n → π*[64] or π → π* transition[65] has been of some controversy. If it is an n → π* transition, the possibility of magnetic dipole–electric dipole coupling of the carboxylate group with the SA chromophore cannot be excluded. It is reasonable to assume, however, that electric dipole–dipole coupling is operative. The electric transition moments of the doubly degenerate π → π* transition of the carboxylate group[61] at 210 nm, or at shorter wavelength if the 210-nm band is an n → π* transition, will form components along and perpendicular to the group's symmetry axis. The perpendicular component is deemed ineffective because of rotational

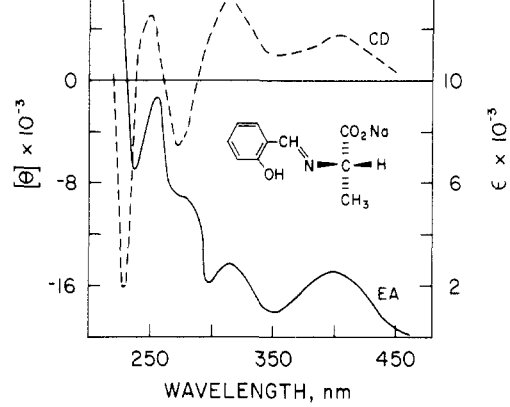
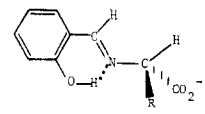


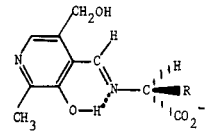
Figure 7. Electronic absorption (EA) and circular dichroism (CD) spectra of L-alanine (L-**19a**) with a 15% molar excess of sodium salicylaldehyde (**8**) in methanol.

averaging about the axis. The sign of bands I and II in the CD spectrum of an aliphatic α-amino acid derivative can be predicted from the preferred chirality that the attachment bond of the carboxylate group has with the phenyl group–methine carbon bond in the SA chromophore. Since the most important conformer contributing to the CD spectrum of the *N*-salicylidene derivative of an aliphatic L-α-amino acid (**20**) is analo-

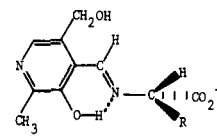


20

gous to that of an α-phenylalkylamine derivative (section IIIB1), the *N*-salicylidene derivatives of L-**19a–h** display positive CEs for bands I and II.[35,42] A recent carbon-13 and proton nuclear magnetic resonance (^{13}C and ^1H NMR) study[66] of the conformations of the pyridoxal Schiff bases of L-α-amino acids gives the predominance of conformer **21a** and/or **21b** for these derivatives, and a conformation analogous to **20** may be a better representation of the preferred conformation about the carbon–nitrogen single bond. When a con-



21a



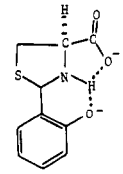
21b

former analogous to **21a** or **21b** for the preferred conformer of an *N*-salicylidene derivative of an aliphatic L-α-amino acid is used, the SA chirality rule predicts positive CEs for both bands I and II.

In the *N*-salicylidene derivatives of aliphatic L-α-amino acid derivatives, the CD maximum near 229 nm, bathochromically shifted from the corresponding EA maximum (Figure 7), is interpreted as the long-wavelength portion of a couplet resulting from exciton splitting between band III of the SA chromophore and the carboxylate group transition since both occur near 215 nm.

A β-hydroxyl substituent on an aliphatic α-amino acid derivative has little effect on its CD spectrum, and those of the *N*-salicylidene derivatives of L-serine (L-**19i**) and L-threonine (L-**19j**) are essentially the same as that of the *N*-salicylidene derivative of L-**19a**. A sulfur-containing substituent at the β position, however, has a dramatic effect. The sign of band I in the spectrum of the L-*S*-methylcysteine (L-**19k**) derivative (Table I) is opposite in sign to that of band I in the spectrum of the L-alanine (L-**19a**) derivative, no CD maximum near 275 nm was detected, and band II is a couplet with a negative longer wavelength component.[35] These changes are a consequence of an additional interaction of the SA chromophore with the sulfide group. A similar interaction in the L-methionine (L-**19l**) derivative only partially compensates for the carboxylate group contribution since the sulfide group is separated from the SA chromophore by an additional σ bond. Except for a reduced intensity for band I, the CD spectrum of the *N*-salicylidene derivative of L-**19l** is the same as that for the derivative of L-alanine (L-**19a**).[35] The couplet structure for band II in the derivative of L-*S*-methylcysteine (L-**19k**) confirms this interpretation. The longest wavelength transition of the sulfide group is at about 240 nm and is electric dipole forbidden but magnetic dipole allowed.[67] The absence of a couplet structure for band II in the CD spectrum of the L-methionine (L-**19l**) derivative is further evidence that the sulfide group–SA chromophore interaction has been weakened by the intervention of an additional σ bond.

A solution of L-cysteine (L-**19m**) with a slight excess of 2 equiv of sodium salicylaldehyde (**8**) was also examined.[35] No CD maximum associated with band II was detected. The unusual nature of this CD spectrum may result from the formation of **22**, analogous to a



22

compound detected in the ^1H NMR spectrum of the reaction product of pyridoxal (**3**) with cysteine (L-**19m**) in alkali.[45] In similar ^1H NMR studies, L-serine (L-**19i**) and L-threonine (L-**19j**) formed normal Schiff bases with **3**, and no intramolecular cyclization product was observed.[45]

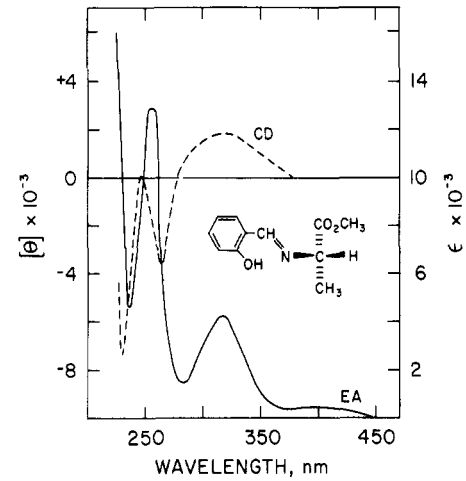
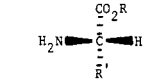


Figure 8. Electronic absorption (EA) and circular dichroism spectra of methyl L-alaninate hydrochloride (L-**23a**·HCl) with a 15% molar excess of sodium salicylaldehyde (**8**) in methanol.

5. Aliphatic α-Amino Esters

The CD spectra of the *N*-salicylidene derivatives of a number of aliphatic α-amino esters (L-**23a–d**) are



L-**23a**, R = R′ = CH_3
b, R = CH_3; R′ = $(CH_3)_2CH$
L-**23c**, R = CH_3; R′ = $(CH_3)_2CHCH_2$
d, R = CH_3CH_2; R′ = $(CH_3)_2CHCH_2$

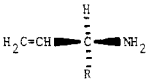
typified by that of the derivative of methyl L-alaninate (L-**23a**) in which maxima for bands I, II, and III are observed (Table I) (Figure 8).[35] The negative maximum at 262 nm is assigned to band II rather than to the quinoid form (**10**) since the maximum persists when the CD spectrum of the isolated *N*-salicylidene derivative of L-**23c** is examined in hexane.[35] This CE may also arise in part from the weak transition at about 275 nm in the EA spectrum of carboxylic esters.[62]

For the *N*-salicylidene derivatives of chiral α-amino esters the dominant interaction for generation of the CEs is coupling of the transition moments of the SA chromophore with those of the alkoxycarbonyl group. Since the conformational preference of the latter group about its attachment bond is not well understood and a symmetry axis for the group is absent, the signs of the observed CEs in the CD spectra cannot be predicted by using the SA chirality rule. These spectra may be compared with those of other aliphatic α-amino ester derivatives for the establishment of their absolute configurations.

6. 1-Alkyl-2-propynylamines and 1-Alkyl-2-propenylamines

The *N*-salicylidene derivatives of (*S*)-1-alkyl-2-propynylamines [(*S*)-**24a–d**] and (*S*)-1-alkyl-2-propenylamines [(*S*)-**25a–c**] show CD spectra with multiple CEs[31] that arise from the interaction of the SA chromophore with the lowest energy $\pi \rightarrow \pi^*$ transition of the ethynyl group at about 152 nm[68] and of the ethenyl group at about 162 nm.[68] The CD spectrum of the *N*-salicylidene derivative of (*S*)-1-methyl-2-

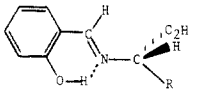
(*S*)-**24a**, R = H; R′ = CH_3
b, R = H; R′ = CH_3CH_2
c, R = H; R′ = $CH_3CH_2CH_2$
d, R = CH_3; R′ = CH_3CH_2



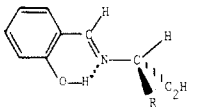
(*S*)-**25a**, R = CH_3
b, R = CH_3CH_2
c, R = $CH_3CH_2CH_2$

propynylamine [(*S*)-**24a**] (Table I) is typical for those of the derivatives of (*S*)-**24a–d** and (*S*)-**25a–c**, and the positive maxima at 316 and 251 nm are easily identified as bands I and II, respectively. The sign of these maxima can be correlated with the absolute configuration by using the SA chirality rule. In propynes and propenes, the electric transition moment of the lowest $\pi \rightarrow \pi^*$ transition is directed along the multiple bond,[68] and thus the sign of the CEs associated with bands I and II is the same as the chirality that the triple and double bonds have with the phenyl group–methine bond.

For the *N*-salicylidene derivatives of the (*S*)-1-alkyl-2-propynylamines [(*S*)-**24a–d**] the ^1H NMR spectra, in which the methine proton of the SA group is seen as a doublet (J = 1.6 Hz),[31] suggest a preferred conformation depicted as **26a**. This preferred conformation is different from an alternate one (**26b**) analogous to that for an *N*-salicylidene-α-phenylalkylamine (**14a**) (section IIIB1) in which the hydrogen atom at the chiral center eclipses the carbon–nitrogen double bond of the SA group. The chirality of the relevant transition moments in both **26a** and **26b**, however, is positive, and the *N*-salicylidene derivative (**26a**, R = CH_3) of (*S*)-1-methyl-2-propynylamine [(*S*)-**24a**] shows positive CEs for bands I and II.[31] The preferred conformation of an *N*-salicylidene-1-alkyl-2-propynylamine will be either **26a** or **26b** dependent on the effective bulk size of the R group in **26**, and thus (*S*)-**24b,c** also show positive CEs for bands I and II.[31] Since an ethyl group is larger in effective bulk size than a methyl group, the *N*-salicylidene derivative of (*S*)-**24d** should have a preferred conformation analogous to **26a** or **26b**, the methyl and ethyl groups replacing the hydrogen atom and the R group, respectively. Thus, positive CEs for bands I and II are observed[31] for the *N*-salicylidene derivative of (*S*)-**24d**.

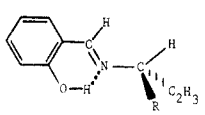


26a

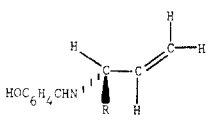


26b

In the ^1H NMR spectra of the *N*-salicylidene derivative of the (*S*)-1-alkyl-2-propenylamines [(*S*)-**25a–c**], the methine proton of the SA group appears as a singlet,[31] indicating a preferred conformation (**27**) such that the hydrogen atom at the chiral center is eclipsed by both the carbon–nitrogen (**27a**) and carbon–carbon double bonds (**27b**).[69] For the configuration shown in **27**, the chirality of the relevant transition moments is positive, and positive CEs are observed for the *N*-salicylidene derivatives of (*S*)-1-methyl-2-propenylamine [(*S*)-**25a**] (Table I) and (*S*)-**25b,c**.[31]



27a

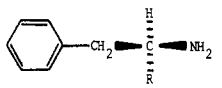


27b

C. One Unsaturated Group Vicinal to the Amino Group

1. α-Benzylalkylamines

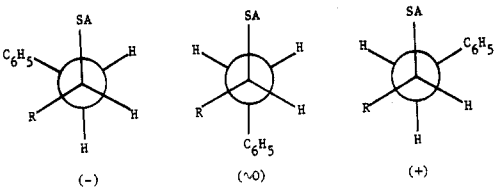
The CEs at 312 and 251 nm in the CD spectrum of the *N*-salicylidene derivative of (*S*)-α-benzylethylamine [(*S*)-**28a**] (Table I) are the result of the coupling of the



(*S*)-**28a**, R = CH_3
(*R*)-**28b**, R = $HOCH_2$
(*S*)-**28c**, R = $(CH_3)_3C$

electric transition moments of the SA group with the ^1L_a and ^1B_a transition moments of the phenyl group, and the sign of these CEs is deduced by conformational analysis.

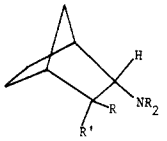
The three conformers of lowest energy for an *N*-salicylidene-α-benzylalkylamine of configuration **29** (*S* configuration for R = CH_3) are depicted as **29a–c**. For each conformer, the sign, as shown, of its contribution to the sign of the observed CEs of bands I and II is determined by the chirality of the attachment bonds of the SA and phenyl groups. The transition moments of bands I and II of the SA chromophore do not deviate greatly from the phenyl group–methine carbon bond (Figure 4), which in turn is parallel to the SA group attachment bond. The effective direction of these moments then can be considered to be along the SA group attachment bond. The effective $\pi \rightarrow \pi^*$ electric transition moments of the phenyl group are also aligned along its attachment bond. Since conformer **29a** is that of highest energy due to steric interaction and conformer **29b** contributes negligible rotational strength due to the anticollinearity and/or large separation between the transition moments, conformer **29c** is the principal contributor to the CD spectrum. In conformer **29c**, the chirality of the attachment bonds of the SA chromophore and the phenyl group is positive (right-handed screw) and positive CEs near 315 and 255 nm are observed for the *N*-salicylidene derivatives of (*S*)-α-benzylethylamine[11,35] [(*S*)-**28a**] (Table I) and (*R*)-**28b**.[41]



29a **29b** **29c**

The effective bulk size of the alkyl group at the chiral center in **29** should have no effect on the sign of the CEs associated with bands I and II, and it may be safely predicted that the *N*-salicylidene derivative of (*S*)-3,3-dimethyl-1-phenyl-2-butylamine [(*S*)-**28c**] will show positive CEs near 315 and 255 nm since the principal contributor to these CEs will be conformer **29c** [R = $(CH_3)_3C$].

The configuration assigned to the conformationally rigid (2*S*)-*exo*-3-phenyl-*endo*-2-norbornanamine [(2*S*)-**30a**], in agreement with subsequent chemical



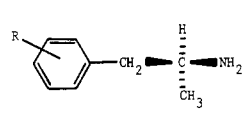
(2*S*)-**30a**, R = C_6H_5; R′ = H
b, R = H; R′ = C_6H_5

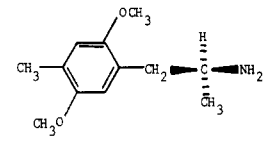
work,[70] was originally based on the CD spectrum off its *N*-salicylidene derivative.[12] It is easily seen that in the derivative of (2*S*)-**30a** the chirality of the SA and phenyl group attachment bonds is positive, and positive CEs for bands I and II are observed.

Application of the SA chirality rule to the derivative of (2*S*)-*endo*-3-phenyl-*endo*-2-norbornanamine [(2*S*)-**30b**] is difficult in that the attachment bonds of the SA and phenyl groups are almost coplanar. Using a molecular model for the *N*-salicylidene derivative of (2*S*)-**30b** and placing the transition moments at the centers of both phenyl rings and along their long axes, a positive, albeit small, chirality results. On this basis the enantiomer of **30b** used to form the *N*-salicylidene derivative showing positive CEs near 315 and 255 nm[12] was assigned the 2*S* configuration.[28]

2. Ring-Substituted α-Benzylalkylamines

The CD spectra for the *N*-salicylidene derivatives of ring-substituted (*S*)-α-benzylethylamines [(*S*)-**31a–e**]





(*S*)-**31a**, R = *o*-Cl
b, R = *m*-Cl
c, R = *p*-Cl
d, R = *p*-NO_2
e, R = *p*-NH_2
f, R = *p*-CF_3
g, R = *m*-CF_3

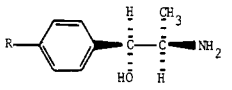
(*S*)-**32**

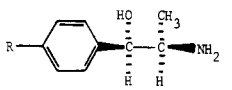
of established configuration show positive CEs for bands I and II,[16,28,30] similar to those shown for (*S*)-α-benzylethylamine[11,35] [(*S*)-**28a**]. The sign of these CEs is in accord with that predicted by the SA chirality rule, since ring substitution at any position only changes the magnitude of the $\pi \rightarrow \pi^*$ electric transition moment components along the phenyl group attachment bond. The derivative of (*S*)-α-(*p*-nitrobenzyl)ethylamine [(*S*)-**31d**] exhibits exciton splitting for CD band II[28] (Table I) since the *p*-nitrobenzyl group has a charge-transfer band (^1L_a transition) very close to 260 nm. The small negative CD band at 291 nm in the spectrum of this derivative is attributed to the ^1L_b transition of the benzene ring of the amine moiety.

The SA chirality rule has also been applied to establish the configuration of the para-substituted α-benzylethylamine (*S*)-**31f**.[40] The assignment of the *S* configuration to the chiral anoretic agent, fenfluramine, made earlier on the basis of a comparison of the CD spectrum of the *N*-salicylidene derivative of norfenfluramine [(*S*)-**31g**] with that of the *N*-salicylidene derivative of (*S*)-α-benzylethylamine[24] [(*S*)-**28a**], is confirmed. The configurational assignment made on this same basis for the enantiomers of the psychotomimetic amine **32**[26] is also confirmed.

3. Norephedrine and Its Derivatives

Application of the SA chirality rule as applied to the *N*-salicylidene derivatives of α-benzylalkylamines may be extended to biologically important norephedrine[71] [(α*R*,β*S*)-**33a**] and norpseudoephedrine [(α*R*,β*R*)-**34a**]

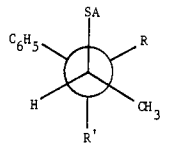


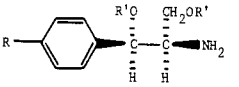


(α*R*,β*S*)-**33a**, R = H
b, R = Cl
c, R = OH

(α*R*,β*R*)-**34a**, R = H
b, R = Cl
c, R = OH

and to their ring-substituted derivatives (α*R*,β*S*)-**33b,c** and (α*R*,β*R*)-**34b,c**.[16,37] Thus for the *N*-salicylidene derivative of (α*R*,β*S*)-**33a**, the conformer making the most important contribution to the CD is **35a**, and





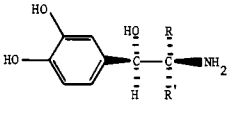
35a, R = H; R′ = OH
b, R = OH; R′ = H

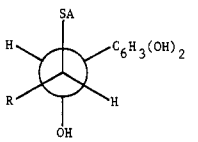
(1*R*,2*R*)-**36a**, R = R′ = H
b, R = O_2N; R′ = CH_3CO

negative CEs for bands I and II are observed.[16] On the reasonable assumption that an hydroxyl group is smaller in effective bulk size than a phenyl group, the dominant conformer for the *N*-salicylidene derivative of (α*R*,β*R*)-**34a** is **35b**, and negative CEs for bands I and II are predicted and are observed.[16] Negative CEs are also observed for the derivative of (1*R*,2*R*)-2-amino-1-phenylpropane-1,3-diol[41] [(1*R*,2*R*)-**36a**]. Since ring substitution has no effect on the sign of the observed CEs (section IIIC2), the enantiomers of **33b,c** and **34b,c** for which the *N*-salicylidene derivatives show negative CEs were assigned the α*R* configuration.[16,37] A prediction, on a similar basis, of the observed negative CEs for the *N*-salicylidene derivative of (1*R*,2*R*)-*O*,*O*′-diacetyl-2-amino-1-(*p*-nitrophenyl)propane-1,3-diol[19] [(1*R*,2*R*)-**36b**] is also in agreement with the SA chirality rule.

4. Norepinephrine and Its Derivatives

The configuration of primary catechol amines such as norepinephrine [(*R*)-**37a**] can also be correlated with the CD spectrum of its *N*-salicylidene derivative even though the amino group is not attached to a chiral center. For the derivative of (*R*)-**37a**, the most important conformer for dichroic absorption is **38a**, and thus positive CEs for bands I and II are predicted and observed.[39] For the *N*-salicylidene derivative of





(*R*)-**37a**, R = R′ = H
(α*S*,β*R*)-**37b**, R = H; R′ = CH_3
(α*R*,β*R*)-**37c**, R = CH_3; R′ = H

38a, R = H
b, R = CH_3

TABLE II. Circular Dichroism Data for the *N*-Salicylidene Derivatives of Some Chiral Amines with Two or More Unsaturated Groups Geminal or Vicinal to the Amino Group

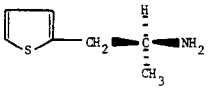
amine	R	R′	CD max,[a] λ, nm ([θ][b]) band I	other	band II	ref
(*S*)-**40a**	$C_6H_5CH_2$	C_6H_5		442 (+29) 352 (−810)	271 (−10 000)[c] 265 (−16 000) 259 (−15 000) 254 (−11 000)[d]	13
(α*S*,β*S*)-**40c**	$C_6H_5CH(CO_2$-menthyl)	C_6H_5			272 (−18 000)[c] 267 (−17 000) 262 (−9800)[d,e]	72
(α*R*,β*S*)-**40d**[f]	$C_6H_5CH(CO_2$-menthyl)	C_6H_5	322 (+14 000)	276 (−11 000) 268 (−4500)[d]	263 (+9800)[d] 256 (+22 000)[d] 252 (+24 000)[e]	72
(α*R*,β*R*)-**42**[f]	$C_6H_5CH(CH_2C_6H_5)$	CH_3	313 (−12 000)[g]		258 (−11 000)	13
L-**43a**[f,h]	C_6H_5	CO_2^-	313 (−6000)		277 (−5800)[i]	35
L-**43b**[f,h]	2-C_4H_3S	CO_2^-	313 (−3500)	275 (+1800)[j]		35
L-**43c**[f,h]	*p*-HOC_6H_5	CO_2^-	315 (−8900)		260 (−11 700)	42
L-**43d**[h]	$C_6H_5CH_2$	CO_2^-	313 (−6600)		272 (−14 000)[i] 266 (−18 000)[i] 261 (−19 000) 256 (−17 000)	35
L-**48a**[h]	$C_6H_5CH_2$	CO_2CH_3	316 (−13 000)		261 (−36 000)	35
L-**48c**[f,h,k]	*p*-$O_2NC_6H_4CH_2$	$CO_2CH_2CH_3$	316 (−3400)		268 (−2800) 252 (+4000)	35
L-**49a**[h]	$^-O_2CCH_2$	CO_2^-			254 (−5000)	35
L-**49c**[h]	H_2NCOCH_2	CO_2^-	315 (+1400)		268 (−6000) 248 (+2300)[l]	35

[a] Methanol as the solvent or as otherwise noted. [b] Molecular ellipticity. [c] May also be associated with a transition in addition to the $\pi \rightarrow \pi^*$ transition of the SA chromophore. [d] Shoulder. [e] Additional maxima at shorter wavelength. [f] Enantiomer used. [g] Maximum at 400 nm ([θ] −1900) assigned to the quinoid tautomer. [h] Derivative formed in situ. [i] Also associated with the ^1L_b transition of the phenyl group of the amine moiety. [j] Assigned to a transition of the thienyl group. [k] CEs of low intensity due to incomplete derivative formation. [l] Band III at 229 nm ([θ] −13 000).

(α*S*,β*R*)-**37b**, the chirality of the α carbon atom comes into play, and although the derivative, as is predicted using conformer **38b**, shows positive CD bands I and II,[39] those of the *N*-salicylidene derivative of its diastereomer (α*R*,β*R*)-**37c** are predicted to be negative since the dominant conformer for dichroic absorption is similar to **35b**.

5. Other β-Arylalkylamines

Although the *N*-salicylidene derivatives of only a single β-arylalkylamine, aside from those for which the aryl group is a benzene ring, have been reported,[35] the absolute configuration of these derivatives can be assigned by application of the SA chirality rule since for generation of the CEs the effective component of the transition moments of the $\pi \rightarrow \pi^*$ transitions of an aryl group is along its attachment bond. Thus the *N*-salicylidene derivative of the enantiomer of 1-(2-thienyl)-2-aminopropane (**39**), which shows positive CEs for



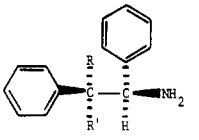
(*S*)-**39**

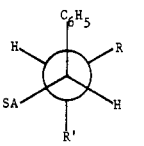
bands I and II, was assigned the *S* configuration.[35]

D. Amines with Two or More Unsaturated Groups

1. Di- and Triphenylalkylamines

For the *N*-salicylidene derivatives of chiral amines that have two or more unsaturated groups, the possibility that each of these groups may couple with the SA chromophore must be taken into account. Thus in the CD spectrum of the (*S*)-α,β-diphenylethylamine [(*S*)-**40a**] derivative in absolute ethanol and methanol strong





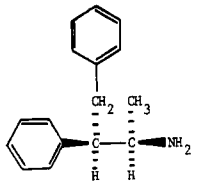
(*S*)-**40a**, R = R′ = H
b, R = H; R′ = C_6H_5
(α*S*,β*S*)-**40c**, R = H; R′ = menthyl-O_2C
(α*R*,β*S*)-**40d**, R = menthyl-O_2C; R′ = H

41a, R = H; R′ = C_6H_5
b, R = menthyl-O_2C; R′ = C_6H_5
c, R = C_6H_5; R′ = menthyl-O_2C

dichroic absorption is associated only with band II of the SA chromophore (Table II).[11,13] In conformer **41a**, the CD contribution of the α phenyl group is positive (section IIIB1) and that of the β phenyl group is negative (section IIIC1), and the algebraic sum of these contributions results in the observed negative CE for band II.

The CD spectrum of the *N*-salicylidene derivative of (*S*)-**40b** also reflects the presence of the three phenyl groups. The derivative shows a number of CEs,[13] but these are difficult to assign, and their signs cannot be predicted with the SA chirality rule.

On the other hand, the CD spectrum of the *N*-salicylidene derivative of (α*R*,β*R*)-β,γ-diphenyl-α-methyl-*n*-propylamine [(α*R*,β*R*)-**42**] is typical for an (*R*)-α-benzylalkylamine derivative (section IIIC1).[13] The γ phenyl group is too remote from the SA chromophore for strong coupling, and the derivative of (α*R*,β*R*)-**42** shows, as is predicted by the SA chirality rule, negative CD maxima for bands I and II (Table



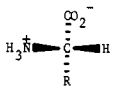
$(\alpha R,\beta R)$-42

II),[13] the sign of these CEs depending only on the configuration at the α carbon atom.

For the two diastereomeric menthyl β-amino-α,β-diphenylpropionate (**40c,d**) *N*-salicylidene derivatives, the presence of the ester group presents an additional complication. With the assumption of only a small contribution from the menthoxycarbonyl group (section IIID3), the CD spectrum of the derivative of (αS,-βS)-**40c** is predicted on the basis of its preferred conformation **41b** to display, as is observed,[72] a CD spectrum (Table II) similar to that of the *N*-salicylidene derivative of (*S*)-**40a**. The contribution of the phenyl group vicinal to the SA chromophore is negative while that of the other phenyl group is positive. For (αR,-βS)-**40d**, however, the geminal phenyl group in the preferred conformation **41c** dos not make a significant contribution to the dichroic absorption, and on the basis of the SA chirality rule as applied to the *N*-salicylidene derivatives of (*S*)-α-phenylalkylamine (section IIIB1), the observed[72] positive CEs for bands I and II (Table II) are predicted.

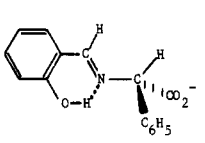
2. α- and β-Aryl α-Amino Acids

In the CD spectra of the *N*-salicylidene derivatives of α- (L-**43a–c**) and β-aryl α-amino acids (L-**43d–f**),[35,42]



L-**43a**, R = C_6H_5 L-**43d**, R = $C_6H_5CH_2$
b, R = 2-thienyl **e**, R = *p*-$HOC_6H_4CH_2$
c, R = *p*-HOC_6H_4 **f**, R = (4-imidazolyl)methyl

formed in situ (section IB), the sign of bands I and II is determined by the chirality of the interaction of the chromophore with the aryl group, which overshadows that with the carboxylate group.[35] Since conformer **44**



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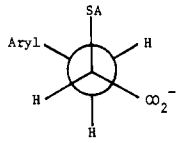
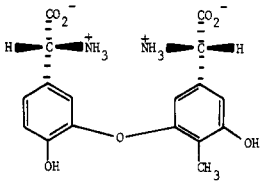


45

is the most important for dichroic absorption, band I is negative in the CD spectrum of the Schiff base derivative of L-phenylglycine[35] (L-**43a**) (Table II). In this spectrum, the negative CD maximum at 277 nm was assigned to the quinoid form (**10**)[35] but is probably associated with the ^1L_b transition of the benzene ring and/or band II of the SA chromophore. In the derivative of L-**43b**, band I is negative (Table II) and a 272-nm band is positive[35] and is assigned to the transition of the thienyl group. For this derivative, no CD band at shorter wavelength was observed, but for that of L-**43c**, the CD spectrum (Table II) shows a strong negative CD maximum at 260 nm assigned as band II and of the same sign as that of band I.[42]

Conformer **45** is the most important contributor to the dichroic absorption for bands I and II of the *N*-salicylidene derivatives of L-β-aryl α-amino acids (L-**43d–f**) such as L-phenylalanine (L-**43d**),[35,66] and as in the spectrum of the derivative of L-**43d** (Table II), bands I and II are negative.[35]

Examination of the CD spectra of the *N*-salicylidene derivatives of some of the α-amino acids from the aglycon of the antibiotic ristocetin A allowed their absolute configurations to be established.[42] Hydrolysis of the aglycon in hydrochloric acid gave the amino acid **46**. Catalytic reduction of **46** yielded enantiomers of



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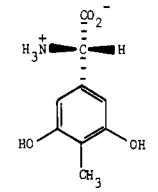
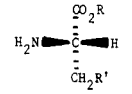


L-**47**

cyclohexylglycine (**19g**) and **47**. The CD spectra of the *N*-salicylidene derivatives of these amino acids were, respectively, enantiomeric to that of L-**19g** and the same as that of L-phenylglycine (L-**43a**) and were thus assigned the D and L configurations, respectively.[42] Thus, **46** has the configuration shown,[42] and in agreement with this assignment, the *N,N'*-disalicylidene derivative of **46** has a CD spectrum in which only a broad positive maximum centered at 280 nm is observed, rotatory contributions of one chiral center almost canceling that of the other.

3. β-Aryl α-Amino Esters

The sign of CD bands I and II for β-aryl α-amino ester (L-**48a–d**) *N*-salicylidene derivatives are those

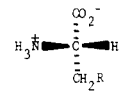


L-**48a**, R = CH_3; R' = C_6H_5
b, R = CH_3; R' = *p*-HOC_6H_4
c, R = CH_3CH_2; R' = *p*-$O_2NC_6H_4$
d, R = CH_3; R' = 3-indolyl

predicted by the SA chirality rule as applied to (*R*)-β-arylalkylamine derivatives (section IIIC), and the derivatives, such as that of methyl L-phenylalaninate (L-**48a**) (Table II), show negative maxima for bands I and II.[11,19,28,35] The couplet for band II in the spectrum of that of ethyl L-*p*-nitrophenylalaninate (L-**48c**) (Table II) is a consequence of dipolar interaction between the transition moments of band II and that of the bathochromically shifted ^1L_a transition of the *p*-nitrophenyl group near 260 nm.[35]

4. Dicarboxylic α-Amino Acids

The CD spectra of the *N*-salicylidene derivatives of chiral, dicarboxylic α-amino acids (**49a,b**), formed by mixing the α-amino acid in methanol with a slight excess of 2 equiv of sodium salicylaldehyde (**8**), again illustrate the effect of two groups that interact with the SA chromophore. For the derivative of L-aspartic acid (L-**49a**), the interaction of the α carboxylate group makes a positive contribution to the CD of bands I and II whereas that of the β carboxylate group is negative. In the CD spectrum of the derivative (Table II) band II is negative,[35] indicating that at least for band II, the



L-49a, R = HO_2C
b, R = HO_2CCH_2
c, R = H_2NCO

β carboxylate group has the greater influence. In the derivative of L-glutamic acid (L-**49b**), the γ carboxylate group is separated from the SA chromophore by an additional σ bond. No maximum associated with bands I and II was observed. Thus, the influence of the γ carboxylate group with the SA chromophore is still substantial.

The CD spectrum of the *N*-salicylidene derivative of L-asparagine (L-**49c**) (Table II) shows the influence of a β amido group. The sign of band I is positive, but its rotational strength is weak and no 275-nm band was observed. The couplet centered at 255 nm arises from coupling of band II of the SA chromophore with the n $\rightarrow \pi^*$ transition of the amide group.[35]

IV. Applications to Amines without Unsaturated Groups

A. General Considerations

Application of the SA chirality rule to amines without unsaturated groups is not as easy as when an unsaturated group is present, and although the CEs are less intense, application of the rule to amines without unsaturated groups is also based on the coupled oscillator mechanism.[32] For these *N*-salicylidene derivatives, the CEs associated with bands I and II originate from coupling of the transition moments of the SA chromophore with transition moments in the rest of the molecule.[32] The effect due to the polarizability of a C–H bond is assumed to be negligible,[73,74] and C–C and C–O bond transition moments vicinal and homovicinal to the SA chromophore are the dominant contributors to the CEs. Since the polarizability of a C–O bond is smaller than that of a C–C bond,[73,74] the contribution of a vicinal or homovicinal C–O bond is less than that of a corresponding C–C bond.

For the SA chromophore, the transition moment directions of bands I and II, although slightly different in direction, are approximately parallel to the attachment bond of the SA group (Figure 4), and the sign of the contribution to the CEs made by a particular vicinal or homovicinal bond can usually be determined from the chirality that the bond has with the attachment bond of the SA group, a positive contribution for positive chirality (right-handed screw) and a negative contribution for negative chirality (left-handed screw).[32] In cases where the bond and the SA group attachment bond are coplanar, the chirality that the bond has with the transition moments of the SA chromophore (Figure 4) is used.

For carbocyclic (section IVC) and oxacyclic (section IVD) amine derivatives, contributions from C–C and C–O ring bonds can usually be assumed to be nil due to the symmetry of the ring and/or mutual cancellation. This assumption is certainly valid for the chair conformation of the six-membered carbocyclic system but may be poor for a six-membered oxacyclic system or for five-membered rings.

The sign of the observed CEs is the algebraic sum of all bond contributions, and the sign of this sum for a particular configuration can usually be deduced by conformational analysis. When a single C–C bond is vicinal to the SA group its contribution predominates.

In some cases, the interpretation of the CD is complicated by a bisignate CD curve for band II or the CE for band II has a different sign from that of the CE for band I. In the absence of exciton splitting, bisignate CD curves associated with a single electronic transition have been interpreted in terms of conformational equilibria, the oppositely signed maxima being due to different conformers,[75,76] to solvated equilibria involving different solvated species,[75,76] or to vibronic coupling.[77,78]

In vibronic coupling, the bisignate feature of band II is a manifestation of the combined effect of an allowed progression of a totally symmetric vibrational mode and a forbidden progression of a nontotally symmetric vibrational mode whose differential dichroic absorption maximum occurs at shorter wavelength and borrows its intensity from the nearby intense band III.[77,78]

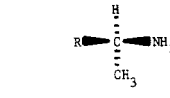
When CEs for bands I and II have different signs, band II or the long wavelength component of band II is used for the configurational correlation since its transition moment is more parallel to the SA group attachment bond (Figure 4), and the larger magnitude and shorter wavelength for band II makes dynamic coupling with C–C and C–O bonds more favorable.

For application of the rule, it is essential that the CE associated with the allowed vibrational mode of band II be identified, and that the algebraic sum of the bond contribution be unambiguous. In some cases, these are not possible, and predictions as to the sign of the CEs for a particular configuration are not certain without use of the CD spectra of model compounds of similar structures and known absolute configurations.

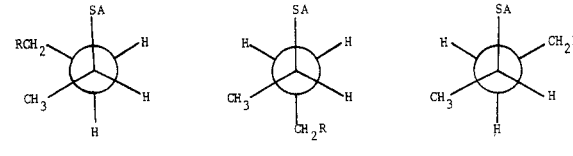
B. Aliphatic Amines

1. 2- and 3-Aminoalkanes

Application of the SA chirality rule to the *N*-salicylidene derivatives of 2-aminoalkanes (**50**) such as



(*S*)-**50a**, R = CH_3CH_2
b, R = $CH_3CH_2CH_2$
c, R = $CH_3(CH_2)_3CH_2$
d, R = $(CH_3)_3C$



51a 51b 51c

(*S*)-2-aminobutane [(*S*)-**50a**] follows from a consideration of its three conformers of lowest energy (**51a–c**, R = H), resulting from rotation about the C(2)–C(3) bond. Conformer **51a** is that of highest energy due to steric interaction and will be unimportant compared to the other two. Conformer **51b** will also contribute negligible rotational strength to the CD spectrum because of the near anticollinearity and large separation of the SA

TABLE III. Circular Dichroism Data for the *N*-Salicylidene Derivatives of Some Chiral Aliphatic Amines

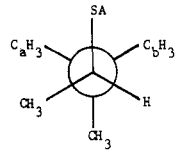
amine	R	R′	solvent[b]	CD max, λ, nm ([θ][a]) quinoid	band I	band II	ref
(*S*)-**50a**	CH_3CH_2	CH_3	M	395 (+630)	313 (+1600)	253 (+4900)	14
(*S*)-**50d**[c]	$(CH_3)_3C$	CH_3	M	400 (+1100)	315 (+2500)	261 (+6200)	14
(*S*)-**54**[c]	$CH_3CH_2CH_2$	CH_3CH_2	M	400 (+590)	316 (+1800)	252 (+2000)[d]	31
55a	3β-hydroxy-5α-androstan-17β-yl	CH_3	D		315 (+10 000)		17
55b	CH_3	3β-hydroxy-5α-androstan-17β-yl	D		315 (−15 000)		17
57	5-methoxy-des-*A*-5,7,9-estratrien-17β-yl	CH_3	D		313 (+13 000)		19
(*S*)-**58a**	$HOCH_2$	CH_3	M	396 (+710)	312 (+2700)	269 (−1900) 248 (+6300)	14
			H[e]		315 (+1800)	267 (−3800) 251 (+8300)	14
(*S*)-**58b**[c]	$HOCH_2$	CH_3CH_2	M	388 (+160)	315 (+450)	267 (−6000) 248 (+2300)	14
			H[f]		316 (−1100)	267 (−6500) 248 (+2900)	14

[a] Molecular ellipticity. [b] M, methanol; D, dioxane; H, *n*-hexane. [c] Enantiomer used. [d] Band III at 220 nm ([θ] −2400). [e] Additional maximum at 420 nm ([θ] −21). [f] Additional maximum at 415 nm ([θ] −120).

group attachment bond and the C(3)–C(4) bond. Conformer **51c** is the principal contributor to the CD spectrum, and the positive chirality that the C(3)–C(4) bond has with the SA group attachment bond unambiguously predicts the observed[14] positive sign for bands I and II for the derivative of (*S*)-**50a** (Table III).

A similar analysis predicts the observed, positive CEs for the *N*-salicylidene derivatives of (*S*)-**50b,c**.[32] In both, conformer **51c** is the principal contributor to the CD spectrum, contributions from the C(4)–C(5) and other C–C bonds being unimportant compared to that of the C(3)–C(4) bond.

The positive sign for CD bands I and II for the derivative of (*S*)-**50d**[14] (Table III) cannot be predicted by using Newman projection **52** without considering the



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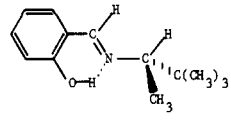

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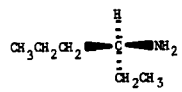
positions of the C_aH_3 and C_bH_3 groups with respect to the transition moments of the SA chromophore. In the preferred conformation of the SA group about its attachment bond[28,35] (**53**), the C_bH_3 group in **52** is closer to the major axis of the chromophore than is the C_aH_3 group. Thus, the positive chirality that the C_bH_3 group attachment bond has with the SA group transition moments makes a greater contribution to the CEs than does the negative chirality that the C_aH_3 group attachment bond has with these moments, and the observed CEs are positive.[14]

For the *N*-salicylidene derivative of (*S*)-3-aminohexane [(*S*)-**54**] the positive CEs[31] (Table III) arise by

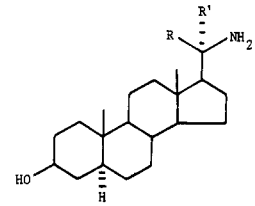


(*S*)-54

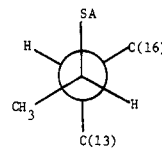
contributions from the C–C bonds vicinal and homovicinal to the SA group. The sum of these contributions is not readily deduced, and no prediction based on the SA chirality rule as to the sign of the CEs for a particular enantiomer is possible.

2. 20-Amino Steroids

The SA chirality rule can also be used to predict the sign of the CE at 315 nm shown by the *N*-salicylidene derivatives of 20-amino steroids. Those with the 20α(*S*) configuration (four reported[17,19]), such as the derivative of 20α-amino-5α-pregnan-3β-ol (**55a**) (Table III), are



55a, R = H; R′ = CH_3
b, R = CH_3; R′ = H



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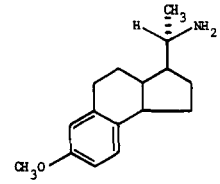
predicted by using Newman projection **56** to show positive CEs for bands I and II, although only a positive CE at 315 nm was reported.[17,19] The other conformers resulting from rotation about the C(17)–C(20) bond in **56** are less stable due to steric interaction and do not make a significant contribution to the CEs. The *N*-salicylidene derivatives with the 20β(*R*) configuration (three reported[17,19]) such as that of 20β-amino-5α-pregnan-3β-ol (**55b**) (Table III) are predicted to show negative CEs for bands I and II, but again only a negative CE at 315 nm was reported.[17,19]

The positive CE near 315 nm shown by the *N*-salicylidene derivative of 20α-amino-5-methoxy-19-nordes-*A*-5,7,9-pregnatriene[19] (**57**) (Table III) is similar



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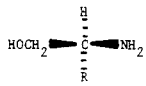
in magnitude to that of the derivative of **55a**, showing

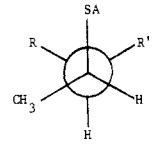
that the benzene ring in the derivative of **57** is too remote from the SA group to have any obvious effect on the CD.

3. β-Amino Alcohols

The CD spectra of the *N*-salicylidene derivatives of (*S*)-2-amino-1-propanol [(*S*)-**58a**] and (*S*)-2-amino-1-butanol [(*S*)-**58b**] (Table III) are unusual in that both show two CEs from 247 to 270 nm.[14]

The conformational mobility of the derivatives and changes in the relative intensities of the CEs with a change in solvent suggest that the two CEs in the 247- to 270-nm region are best explained on the basis of an equilibrium between two conformers having slightly different transition energies for band II.[76]

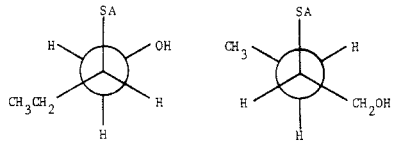




(*S*)-**58a**, R = CH_3 **59a**, R = H; R′ = OH
b, R = CH_3CH_2 b, R = OH; R′ = H

Conformational analysis for the *N*-salicylidene derivative of (*S*)-**58a** suggests that conformer **59a** is the most important contributor to the CD and that the CEs arise by coupling of the SA group transition moments with that of the vicinal C–O bond. The chirality that the latter has with the SA group attachment bond is positive, and positive CEs for bands I and II are predicted in conformity with the observed positive CEs at 312 and 248 nm in methanol and 315 and 251 nm in *n*-hexane[14] (Table III). The negative CE at 269 nm in methanol and 267 nm in *n*-hexane indicates that the contribution due to a less favored negatively contributing conformer **59b** may be significant. Only a slight intensity increase for both bands I and II is to be expected when a polar solvent is changed to a nonpolar solvent (section IIA). For the derivative of (*S*)-**58a**, however, the 2-fold increase in the intensity of the 267-nm, negative CD maximum on changing the solvent from methanol to *n*-hexane is attributed to an increase in the importance of the negatively contributing conformer **59b**.

The CD spectrum of the *N*-salicylidene derivative of (*S*)-**58b** is interpreted in a similar way. In the rotationally important conformer **60**, the contribution to the



60a **60b**

CD from the C–O bond is positive (**60a**) and from the C(3)–C(4) bond is negative (**60b**). Since the contribution from a vicinal C–O bond is less than that from a vicinal C–C bond,[73,74] the *N*-salicylidene derivative of (*S*)-**58b** is predicted to show negative CEs for bands I and II, in agreement with the observed negative CD maxima at 316 and 267 nm in *n*-hexane[14] (Table III). The dependence of the conformation equilibrium on the solvent is dramatically demonstrated by the sign reversal for band I when the solvent is methanol[14] (Table III).

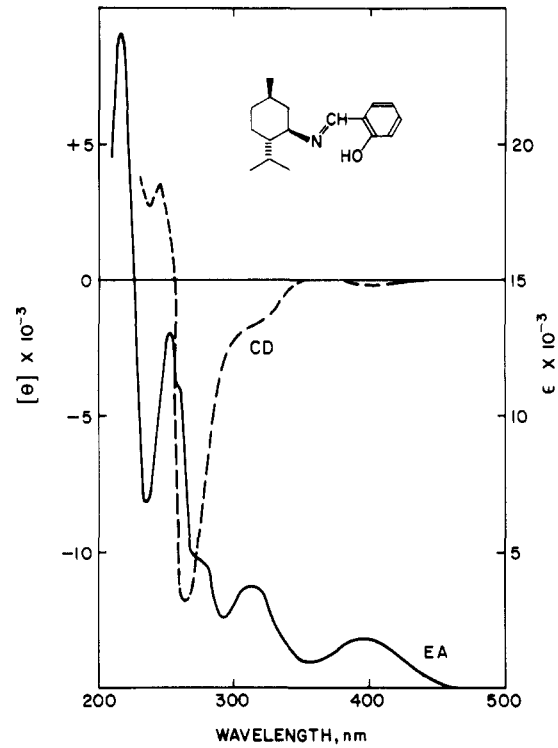
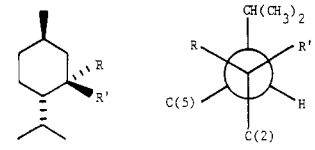


Figure 9. Electronic absorption (EA) and circular dichroism (CD) spectra of the *N*-salicylidene derivative of (3*R*)-menthylamine [(3*R*)-**61a**] in methanol.

C. Alicyclic Amines

1. Terpene Amines

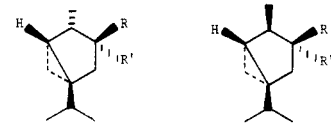
For the *N*-salicylidene derivatives of (3*R*)-menthylamine [(3*R*)-**61a**] and (3*S*)-neomenthylamine [(3*S*)-**61b**], the cyclohexane system has a chair conformation



(3*R*)-**61a**, R = H; R′ = NH_2 **62a**, R = H; R′ = SA
(3*S*)-**61b**, R = NH_2; R′ = H b, R = SA; R′ = H

and the SA group takes preferably an equatorial and an axial orientation, respectively. Thus, for the derivatives of (3*R*)-**61a** and (3*S*)-**61b**, the chirality of the attachment bond of the isopropyl group with that of the SA group is negative (**62a**) and positive (**62b**), respectively, and the CD spectra (Table IV) show respectively negative and positive CEs for bands I and II or the long-wavelength component of band II, band II for the derivative of (3*R*)-**61a** showing a bisignate CD curve (Figure 9), interpreted in terms of vibronic coupling (section IVA).[33]

For the thujylamines (**63**) and the isothujylamines (**64**), the interpretation of the CD spectra of their *N*-



(3*S*)-**63a**, R = NH_2; R′ = H (3*R*)-**64a**, R = H; R′ = NH_2
(3*R*)-**63b**, R = H; R′ = NH_2 (3*S*)-**64b**, R = NH_2; R′ = H

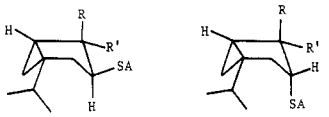
salicylidene derivatives is somewhat more complicated

TABLE IV. Circular Dichroism Data for the *N*-Salicylidene Derivatives of Some Alicyclic Terpene Amines

terpene amine		CD max,[a] λ, nm ([θ][b])			
no.	name	quinoid	band I	band II	ref
(3*R*)-**61a**	(3*R*)-menthylamine	400 (−150)	315 (−1400)[c]	267 (−12 000) 245 (+3500)	33
(3*S*)-**61b**	(3*S*)-neomenthylamine	396 (+860)	314 (+710)[c]	264 (+6500)	33
(3*S*)-**63a**	(3*S*)-thujylamine	398 (+400)	313 (+1700)[d]	264 (+4800)	33
(3*R*)-**63b**	(3*R*)-neothujylamine	398 (−170)	315 (−630)[c]	273 (−2300)[e] 254 (+8800)	33
(3*R*)-**64a**	(3*R*)-isothujylamine	~400 (+)[f]	~315 (+)[f]		33
(3*S*)-**64b**	(3*S*)-neoisothujylamine	398 (−240)[c]	314 (−2000)	254 (−6500)	33
67	*endo*-fenchylamine	400 (+730)	316 (+2700)	259 (+7100)	33

[a] Methanol as the solvent. [b] Molecular ellipticity. [c] Shoulder. [d] Additional shoulder assigned to the quinoid form at 280 nm ([θ] +2800). [e] May be due to the n → π* transition of the azomethine group. [f] Ellipticity measurements not of quantitative significance.

because of the regular (symmetrical) boat[33] or twist-boat conformation[79] of the bicyclic system. For the regular boat conformation, the SA group attachment bond in the derivatives of (3*S*)-thujylamine [(3*S*)-**63a**] and (3*S*)-neoisothujylamine [(3*S*)-**64b**] has a positive (**65a**) and a negative chirality (**65b**), respectively, with the



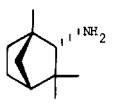
65a, R = H; R′ = CH_3 **66a**, R = H; R′ = CH_3
b, R = CH_3; R′ = H **b**, R = CH_3; R′ = H

vicinal methyl group attachment bond, and positive and negative CEs, respectively, are observed for bands I and II[33] (Table IV).

In the CD spectrum of the *N*-salicylidene derivative of (3*R*)-neothujylamine [(3*R*)-**63b**], the 273-nm maximum was initially assigned to the vibrationally allowed component of band II[33] (section IVA) but may be due to the n → π* transition of the azomethine group[54] (section IIB). Thus, the spectrum of this derivative may be unusual in that band I at 315 nm and band II at 254 nm have opposite signs. The derivative of (3*R*)-**63b**, however, has in a regular boat conformation a small negative dihedral angle for the SA group and methyl group attachment bonds (**66a**), but in a twist-boat conformation,[79] contributions from other carbon–carbon bonds may come into play, making band I negative and band II positive.

In the regular boat conformation of the *N*-salicylidene derivative of (3*R*)-isothujylamine [(3*R*)-**64a**], the attachment bonds of both the vicinal methyl group and the SA chromophore are almost antiparallel to each other (**66b**). As a result, the coupled oscillator contribution of the vicinal methyl group attachment bond is small, and the dichroic absorption associated with bands I and II is weak (Table IV).

The interpretation of the CD spectrum of the *N*-salicylidene derivative of *endo*-fenchylamine (**67**) is



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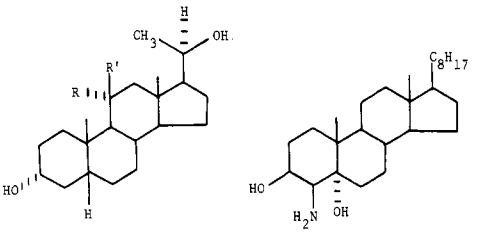
complicated in that the bicyclic system is not symmetrically disposed with respect to the SA group attachment bond. If only the carbon–carbon bonds vicinal to the SA group are considered more of these bonds have positive chirality with the SA group attachment bond, and thus positive CEs for bands I and II are predicted and are observed[33] (Table IV).

2. Steroidal Amines

The *N*-salicylidene derivatives of 11α- (**68a**) and 11β-amino-5β-pregnane-3α,20β-diol (**68b**) show almost



68a, R = NH_2; R′ = H **69**
b, R = H; R′ = NH_2

enantiomeric CD spectra (Table V) that are unusual in that the sign of band I is different from that of band II or the long-wavelength component of band II.[32] The sign of the latter band, however, is the same as the chirality that the vicinal C(9)–C(10) bond has with the SA group attachment bond, negative for the *N*-salicylidene derivative of **68a** and positive for that of **68b**.

Similar correlations are also possible for other cyclic steroidal amine derivatives for which the sign of the observed CE for band II or the long-wavelength component of band II is the same as the chirality (±60° dihedral angle) that a single C–C bond, attached to a six-membered ring bearing the SA group and vicinal to the SA group, has with the SA group attachment bond. The steroidal amine derivatives of this type for which the CD spectra have been reported[25] are those of 1α-, 4β-, 6α-, 6β-, 7α-, and 7β-amino 5α-steroids and a 12α-amino 5β-steroid (nine examples). In all of these spectra, band II or the allowed component of band II is easily identified in that it is the most intense CD maximum in each spectrum. In some of these derivatives, there are hydroxyl groups vicinal to the SA chromophore. In all of these, except that of 4β-aminocholestane-3β,5α-diol (**69**), the hydroxyl groups are anti-trans to the SA group, and the contribution of the C–O bond to the CD is unimportant compared to that of the vicinal C–C bond. In the *N*-salicylidene derivative of **69**, the C-5 hydroxyl group is anti-trans to the SA chromophore, but the C(3)–O bond has a dihedral angle of −60° with the attachment bond of the

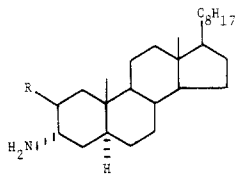
TABLE V. Circular Dichroism Data for the *N*-Salicylidene Derivatives of Some Alicyclic Steroidal Amines

steroidal amine		sol-	CD max, λ, nm ([Θ][a])				
no.	name	vent[b]	quinoid	band I	band II	band III	ref
68a	11α-amino-5β-pregnane-3α,20β-diol	M		318 (+3800)	271 (−18 000) 250 (+9200)	232 (+4400)	32
68b	11β-amino-5β-pregnane-3α,20β-diol	M		324 (−1800)	271 (+13 000)	234 (+2600)	32
69	4β-aminocholestane-3β,5α-diol	D		316 (+10 000)	267 (+17 000)		25
70a	3α-amino-5α-cholestane	M	389 (−820)	315 (−1500)	253 (−4900)		32
70b	3α-amino-5α-cholestan-2β-ol	E	409 (+200)	314 (−1300)	255 (+4100)	~220 (+5600)	25
71	2β-amino-5α-cholestane-1α,3β-diol	D		315 (−6600)	270 (−11 000)[c]		25
72	3β-amino-5α-cholestane	H		315 (+4100)	252 (+5500)		32
73	3α-amino-5β-solanidane	E	405 (−500)	314 (−1800)	250 (−3000)		25
74a	17β-amino-5α-androstan-3β-ol	M	402 (+6600)	315 (+15 000)	254 (+26 000)		32
74b	17α-amino-5α-androstan-3β-ol	D		315 (−15 000)			19
75	16β-amino-5α-androstane	M[d]	395 (−660)	312 (−2100)[e]	251 (−6200)		32

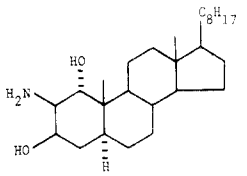
[a] Molecular ellipticity. [b] M, methanol; D, dioxane; E, ethanol; H, hexane. [c] Maximum not reached. [d] Derivative formed in situ. [e] Maximum at 272 nm ([Θ] + 1500) assigned to the n → π* transition of the azomethine group.

SA group. The C(3)–O bond then makes a negative contribution to the CEs, but this contribution does not completely cancel the positive contribution of the C(5)–C(6) bond, and the observed CEs for the *N*-salicylidene derivative of **69** are positive[25] (Table V).

In the *N*-salicylidene derivative of 3α-amino-5α-cholestane (**70a**) there is no C–C or C–O bond attached to ring A that is vicinal to the SA group, and the sign of the CEs for bands I and II is determined by the chirality that a homovicinal C–C bond has with the SA chromophore attachment bond. In the derivative of **70a**, the chirality of the homovicinal C(5)–C(6) bond is



70a, R = H
b, R = OH



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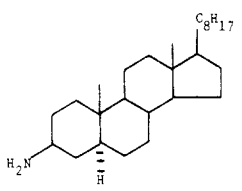
negative (−120° dihedral angle), and negative CEs are observed[32] (Table V). By a similar analysis, the CEs for bands I and II for the *N*-salicylidene derivative of 3α-amino-5α-cholestan-2β-ol (**70b**) are predicted to be negative. For this derivative, however, the sign of band II is reported as positive[25] (Table V). The C(2)–O bond is anti-trans to the SA chromophore and thus makes a negligible contribution to the CEs. Since the observed CEs for the *N*-salicylidene derivatives of **70a** and 3α-amino-5α-solanidane are in agreement with prediction,[25] the CD spectrum of the derivative of **70b** should be verified.

When the contribution of a C–C bond homovicinal to the SA chromophore as deduced for the derivative of **70a** is used, predictions as to the sign of the CEs for bands I and II for a 2β-amino-5α, a 3β-amino-5β, and a 5α-amino steroid or steroidal alkaloid are in agreement with observation.[25]

In the *N*-salicylidene derivative of 2β-amino-5α-cholestane-1α,3β-diol (**71**), the vicinal C(1)–O bond is anti-trans to the axial SA group and makes no contribution to the CEs, but the chirality of the vicinal C(3)–O bond to the SA group attachment bond is positive. Since the CEs for bands I and II are negative[25] (Table V), the negative contribution of the homovicinal C(9)–C(10) bond is then empirically shown to be greater than the positive contribution of the vicinal C(3)–O bond.

For the *N*-salicylidene derivatives of 3β-amino-5α-cholestane (**72**), the C(5)–C(6) bond, homovicinal to the



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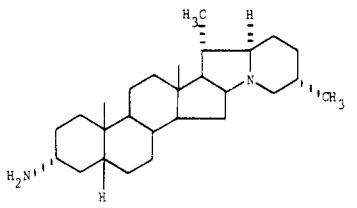

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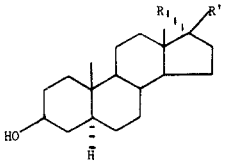
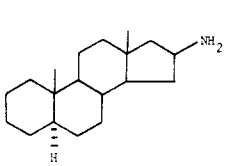
SA group attachment bond, is coplanar with the latter. The chirality of the C(5)–C(6) bond with the transition moments of the SA chromophore is deduced by consideration of the preferred conformation of the SA group about its attachment bond. In this conformation, the methine hydrogen of the SA group eclipses the hydrogen atom at C(3)[13] (section IIIB1), the C(5)–C(6) bond has positive chirality with the long axis of the SA chromophore, and the CD spectrum of **72** shows positive CEs for bands I and II[32] (Table V). A similar analysis predicts the observed[25,32] positive CEs for bands I and II for the *N*-salicylidene derivatives of other 3β-amino-5α steroids and steroidal alkaloids (five examples). On this same basis the negative CEs for the 3α-amino-5β-solanidine (**73**) derivative[25] (Table V) are also predicted.

The CD of the *N*-salicylidene derivative of 17β-amino-5α-androstan-3β-ol (**74a**) (Table V) and three



74a, R = H; R′ = NH_2
b, R = NH_2; R′ = H



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other 17β-amino steroids show positive CEs near 315 and 255 nm associated with bands I and II, respectively.[19,25,32,54] In the spectrum of these derivatives there is usually a weaker, negative CE near 275 nm, assigned to the n → π* transition of the azomethine group[54] and

TABLE VI. Circular Dichroism Data for the *N*-Salicylidene Derivatives of Some Amino Sugars

amino sugar		CD max,[a] λ, nm ([Θ][b])			
no.	name	quinoid	band I	band II	ref
76a	β-D-glucopyranosylamine		318 (−1200)	261 (−10 000)	21
76b	β-D-mannopyranosylamine	405 (+81)	312 (+2500)	252 (+5400)	21
78	methyl 2-amino-2-deoxy-β-D-glucopyranoside		312 (+2300)	260 (+7900)	21
79	methyl 3-amino-3-deoxy-α-D-glucopyranoside		316 (−1800)	254 (−2600)	21
80a	2-amino-2-deoxy-D-glucose	401 (+1700)	313 (+5200)	259 (+11 000)	21
81a	3-*O*-benzyl-6-*O*-triphenylmethyl-1,2-*O*-isopropylidene-5-amino-5-deoxy-α-D-glucofuranose	402 (+630)	320 (+3800)	268 (+4300) 255 (−11 000)	23
81b	3-*O*-benzyl-6-*O*-triphenylmethyl-1,2-*O*-isopropylidene-5-amino-5-deoxy-β-L-idofuranose	400 (−84)	316 (−3500)	258 (−7000)	23

[a] Methanol as the solvent. [b] Molecular ellipticity.

recognized as such because its intensity is substantially less than that of the maximum near 255 nm.

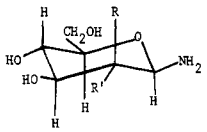
With the assumption of a planar cyclopentane ring and a preferred conformation of the SA group about its attachment bond such that the methine hydrogen atom of the SA group eclipses the hydrogen atom at C-17,[13] the near proximity and positive chirality of the C-(12)–C(13) bond with the SA group transition moments predicts positive CEs for bands I and II of the 17β-amino steroid derivative.

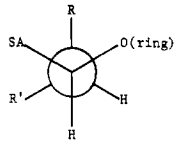
For the *N*-salicylidene derivative of 17α-amino-5α-androstan-3β-ol (**74b**), the chirality that the C(12)–C(13) bond makes with the SA group attachment bond is negative. Since the C(13)–C(18) bond makes only a negligible contribution to the CD, the CE for band I is negative[25] (Table V). The CE associated with band II, however, has not been reported.

The *N*-salicylidene derivative of 16β-amino-5α-androstane (**75**) has negative CEs for bands I and II and a positive maximum at 272 nm for the n → π* transition of the azomethine group[32] (Table V). It is not possible, however, using the SA chirality rule to predict the sign for bands I and II. For another 16β-amino steroid derivative CD band I is reported[25] to be negative while that for a 16α-amino steroid derivative is positive.[25]

D. Amino Sugars

For the *N*-salicylidene derivatives of β-D-glucopyranosylamine (**76a**) and β-D-mannopyranosylamine (**76b**), the CEs associated with bands I and II arise by





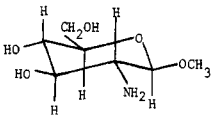
76a, R = H; R′ = OH
b, R = OH; R′ = H

77a, R = H; R′ = OH
b, R = OH; R′ = H

interaction of the vicinal C(2)–O bond with the equatorial SA group, contributions due to other C–C and C–O bonds being negligible. Thus for the derivative of **76a**, the chirality that the vicinal C(2)–O bond has with the attachment bond of the SA group is negative (**77a**), and negative CEs at 318 and 261 nm are observed[21] (Table VI). For that of **76b**, the chirality is positive (**77b**), and positive maxima for bands I and II are observed[21] (Table VI).

The observation that the *N*-salicylidene derivatives of **76a** and **76b**, differing only in the configuration at C-2, show negative and positive CEs, respectively, is in agreement with the conclusion that any contributions from C–C and C–O ring bonds for an equatorial SA group on an oxacyclic system need not be considered.[36]

The mutual cancellation of the vicinal bond contributions in the *N*-salicylidene derivatives of methyl 2-amino-2-deoxy-β-D-glucopyranoside (**78**) necessitates



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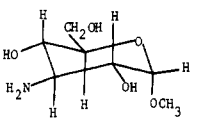

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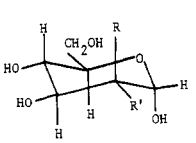
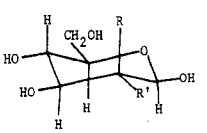
consideration of the contribution of the homovicinal C(4)–O bond. The bond is coplanar with the equatorial 2-SA group. The chirality that the former has with the SA group transition moments is deduced by using the preferred conformation of the SA group about its attachment bond in which the methine hydrogen atom of the SA group eclipses the C-2 hydrogen atom.[13] Since this chirality is positive, the *N*-salicylidene derivative of **78** is predicted to show the observed[21] positive CEs for bands I and II (Table VI). For the *N*-salicylidene derivative of methyl 3-amino-3-deoxy-α-D-glucopyranoside (**79**) substantial cancellation of the homovicinal bond contributions occurs, but since the contribution of the C(5)–C(6) bond is greater than that of the C(1)–O bond, the CEs are predicted to be weakly negative. In agreement with this analysis, the CEs for the derivative of **79** are weakly negative[21] (Table VI).

For the *N*-salicylidene derivatives of 2-amino-2-deoxy-D-glucose (**80a**) and 2-amino-2-deoxy-D-mannose (**80b**), the presence of the α (α-**80a,b**) and β anomers (β-**80a,b**) must be considered. Both anomers for the





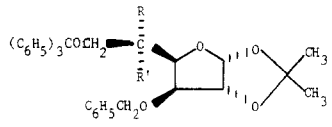
α-**80a**, R = H; R′ = NH_2
b, R = NH_2; R′ = H

β-**80a**, R = H; R′ = NH_2
b, R = NH_2; R′ = H

derivative of **80a** are predicted to show positive CEs, and the overall prediction is in agreement with the observed[21] positive CEs for the derivative of **80a** (Table

VI). The SA group in the derivative of **80b** is preferably in an axial conformation, and the contributions of the ring bonds must be taken into account. Since the sign of the observed CEs is the sum of a number of mutually cancelling C–C and C–O bonds in both anomers, an unambiguous prediction as to the sign of the observed CEs is not possible. That no CE for the *N*-salicylidene derivative of **80b** was observed[21] confirms this assessment.

For the *N*-salicylidene derivatives of other amino sugars, similar predictions[36] are possible and are in agreement with the observed CEs.[21] With still others, such as those of 3-*O*-benzyl-6-*O*-(triphenylmethyl)-5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**81a**) and its C-5 epimer, 3-*O*-benzyl-6-*O*-(triphenylmethyl)-5-amino-5-deoxy-1,2-*O*-isopropylidene-β-L-idofuranose (**81b**), predictions as to the sign of the observed CEs are not possible because of the many bond contributions present. It is to be noted that the *N*-salicylidene derivatives of **81a** and **81b** show essentially



81a, R = NH_2; R′ = H
b, R = H; R′ = NH_2

enantiomeric CD spectra with a positive CE at 320 nm for that of **81a** and a negative one at 316 nm for that of **81b**[23] (Table VI). The derivative of **81b**, however, displays a bisignate curve for band II, possibly due to different conformational diastereomers for this derivative.

V. Acknowledgments

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