# CD-Spectroscopic Confirmation of the Absolute Configuration of a Conformationally Flexible Aldehyde Ester Containing a Quarternary Stereogenic Center

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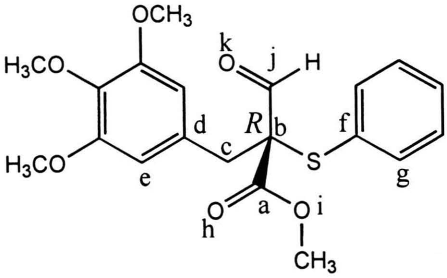
The absolute configuration of the conformationally flexible aldehyde ester methyl-2-formyl-2-(phenylsulfanyl)-3-(3,4,5-trimethoxyphenyl)-propanoate was determined by comparison of measured and calculated CD spectra.

The spectra were calculated by means of the so-called matrix method assuming R configuration at the stereogenic center. Calculated and observed signs of the first three most intense CD bands agree. Therefore, it was concluded that the absolute configuration of the compound was also *R*, which is in perfect agreement with the results of an X-ray structure determination.

## 1. Introduction

The SAMP/RAMP-hydrazone method has been used efficiently to synthesize polyfunctional molecules bearing a quarternary stereogenic center, which can be used as building blocks in the asymmetric synthesis of natural and bioactive compounds [1, 2].



Scheme 1.

The absolute configuration of the substituted aldehyde ester **1** shown in Scheme 1 was determined by means of solid state X-ray crystallography [1]. While standard X-ray structure determinations require single crystals of sufficient quality, there are many compounds which, inspite of all efforts, crystallize poorly or even not at all. Consequently, the structure of such compounds cannot be elucidated by this analytical method. Thus it is highly desirable to have a method that allows determination of the absolute configuration in solution. Because the Cotton effects of two enantiomers differ in their signs, such a tool is provided by the combination of experimental and theoretical CD spectroscopy. Within the framework of this approach the experimentally determined CD spectrum of an enantiomerically pure compound with unknown absolute configuration is compared with the spectrum calculated for one of the enantiomers. This method was already successfully applied in a number of other cases [3 - 6]. As a further test of this approach it was now used to determine the absolute configuration of aldehyde ester **1** (cf. Scheme 1). The high conformational flexibility of this compound was taken into account by including several conformers, differing in the orientation of the side chains.

## 2. Computational methods

Starting from the experimentally determined atomic coordinates of **1**, an initial set of structural parameters was generated by performing a complete geometry optimization with the semiempirical AM1 method [7, 8] as implemented in the MOPAC 6.0 set of quantum chemical routines [9]. 63 further conformers were then generated from the resulting structural

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Table 1. Heats of formation $\Delta H_f(i)$, in kcal/mol), dihedral angles ($\vartheta_n(i)$, in degr.), and Boltzmann factors ($f_B(i)$, in %) of the 16 most stable conformers of compound **1**.

| $i$ | $\Delta H_f(i)$ | $\vartheta_1(i)$ | $\vartheta_2(i)$ | $\vartheta_3(i)$ | $\vartheta_4(i)$ | $\vartheta_5(i)$ | $\vartheta_6(i)$ | $f_B(i)$ |
|---|---|---|---|---|---|---|---|---|
| **1a** | −165.148 | 126.3 | −29.9 | 175.9 | 91.7 | 103.6 | 101.0 | 14.76 |
| **1b** | −165.093 | 126.4 | −29.6 | 176.4 | −90.3 | 103.6 | −78.2 | 13.45 |
| **1c** | −164.722 | −126.7 | 27.9 | 177.5 | 89.8 | 93.7 | −87.4 | 7.19 |
| **1d** | −164.717 | 61.4 | 26.6 | 177.0 | 89.4 | 93.4 | −86.9 | 7.13 |
| **1e** | −164.648 | 61.7 | 27.2 | 177.8 | −92.2 | 93.4 | −86.9 | 6.34 |
| **1f** | −164.638 | −126.8 | 28.0 | 177.9 | −92.3 | 93.7 | −87.5 | 6.24 |
| **1g** | −164.451 | −154.7 | 169.5 | 170.5 | 90.1 | 95.5 | −65.7 | 4.55 |
| **1h** | −164.347 | −151.5 | 167.4 | 171.7 | −91.9 | 95.0 | −66.9 | 3.82 |
| **1i** | −164.198 | 76.7 | −164.7 | 173.4 | 90.4 | 95.5 | −61.6 | 2.97 |
| **1j** | −164.108 | 75.2 | −167.4 | 173.5 | −91.9 | 95.4 | −61.4 | 2.55 |
| **1k** | −163.989 | 61.4 | 27.8 | 179.1 | −91.8 | 90.6 | 97.4 | 2.08 |
| **1l** | −163.975 | −149.2 | 162.2 | 178.0 | −91.7 | 82.9 | 105.4 | 2.04 |
| **1m** | −163.963 | 41.3 | 159.4 | 178.1 | −91.9 | 83.9 | 103.4 | 1.99 |
| **1n** | −163.948 | −127.3 | 28.4 | 179.4 | −91.7 | 90.8 | 97.1 | 1.95 |
| **1o** | −163.929 | 123.0 | −22.7 | −179.6 | −89.9 | 95.9 | 98.7 | 1.88 |
| **1p** | −163.908 | 41.9 | 158.7 | 177.8 | 89.8 | 83.8 | 102.5 | 1.82 |

parameters by systematically varying the six dihedral angles Cb-S-Cf-Cg($\vartheta_1$), Cc-Cb-S-Cf($\vartheta_2$), Cd-Cc-Cb-S($\vartheta_3$), Ce-Cd-Cc-Cb($\vartheta_4$), S-Cb-Cj-Ok($\vartheta_5$), and S-Cb-Ca-Oh($\vartheta_6$) (cf. Scheme 1). The obtained sets of coordinates were subsequently used as starting parameters in geometry optimizations without constraints. In this way we obtained a total number of 64 conformers which were all included into the calculation of the CD spectrum. The optimized dihedral angles ($\vartheta_1(i)$ – $\vartheta_6(i)$) of the sixteen most stable isomers (**1a** - **1p**) together with the corresponding heats of formation ($\Delta H_f(i)$), are listed in Table 1. $f_B(i)$ is the Boltzmann factor of conformer *i*, determining the contribution of the spectrum of this isomer to the total CD spectrum.

The CD spectra of these conformers were calculated by means of the so-called matrix method [10] using a computer program developed in our laboratory [11 - 13]. In this method the molecule is divided into groups and the cleaved bonds are saturated with hydrogen atoms. The geometries of the resulting group molecules are optimized with the AM1 method. The calculations of the corresponding group parameters like, e. g., transition energies and transition moments, are performed with the semiempirical CNDO/2S method as implemented in the DZDO/MCD3SP program package [14]. Wave functions for the total molecule are then calculated by a procedure in which products of group functions are used as basis set. One basis function is the product of the ground state functions of the groups. In the other functions of the basis set, one of the ground state functions is replaced by an excited state function of the corresponding group. We did not take into account those basis functions where two or more ground state functions are replaced. Elements of the Hamiltonian matrix between the product of ground state functions and the other basis functions are assumed to be zero [10, 12]. The diagonal elements are set equal to the corresponding transition energies of the unperturbed groups [10, 12]. The non-diagonal elements are calculated using the monopole-monopole-

Table 2. Calculated ($\lambda_{cal}$) and observed ($\lambda_{obs}$) absorptions of the model chromophors of aldehyde ester **1**.

| Model chromophor | $\lambda_{cal}$/nm | $\lambda_{obs}$/nm | Ref. |
|---|---|---|---|
| acetaldehyde | 396.2<br>167.9<br>148.5 | 290 | [15] |
| methyl acetate | 339.5<br>169.2<br>152.5 | 209.7 | [16] |
| thiophenol | 271.9<br>228.4<br>199.8<br>195.4<br>195.2<br>183.2 | 269<br>236 | [17]<br>[17] |
| 1,2,3-trimethoxybenzene | 288.9<br>239.2<br>210.2<br>205.3<br>185.3<br>177.5 | 267 | [18] |

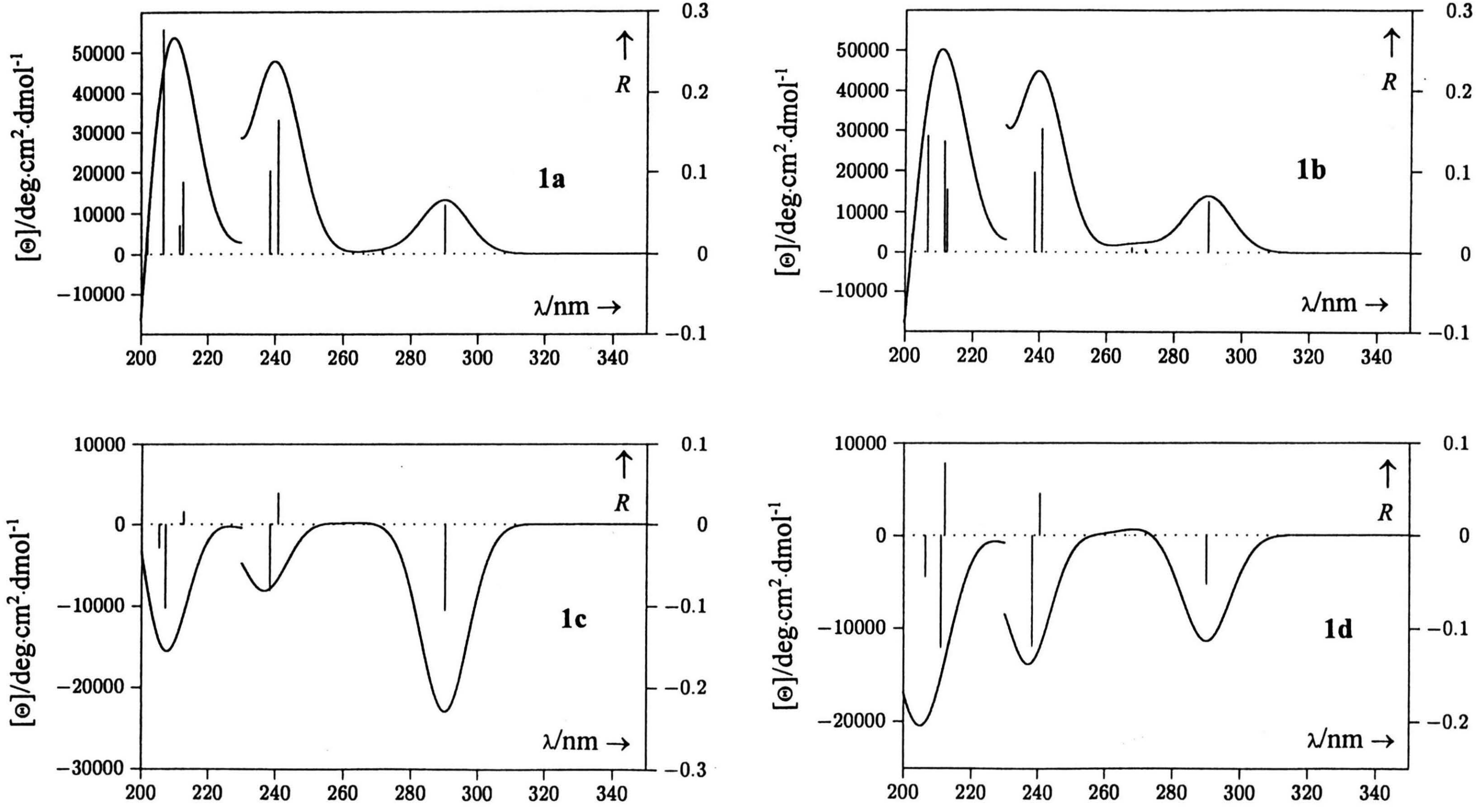

Fig. 1. Calculated CD spectra ([*Θ*]) and rotational strengths (*R*, represented as bars) of the four most stable conformers (**1a** - **1d**) of aldehyde ester **1**. Below 230 nm the calculated quantities were divided by ten.

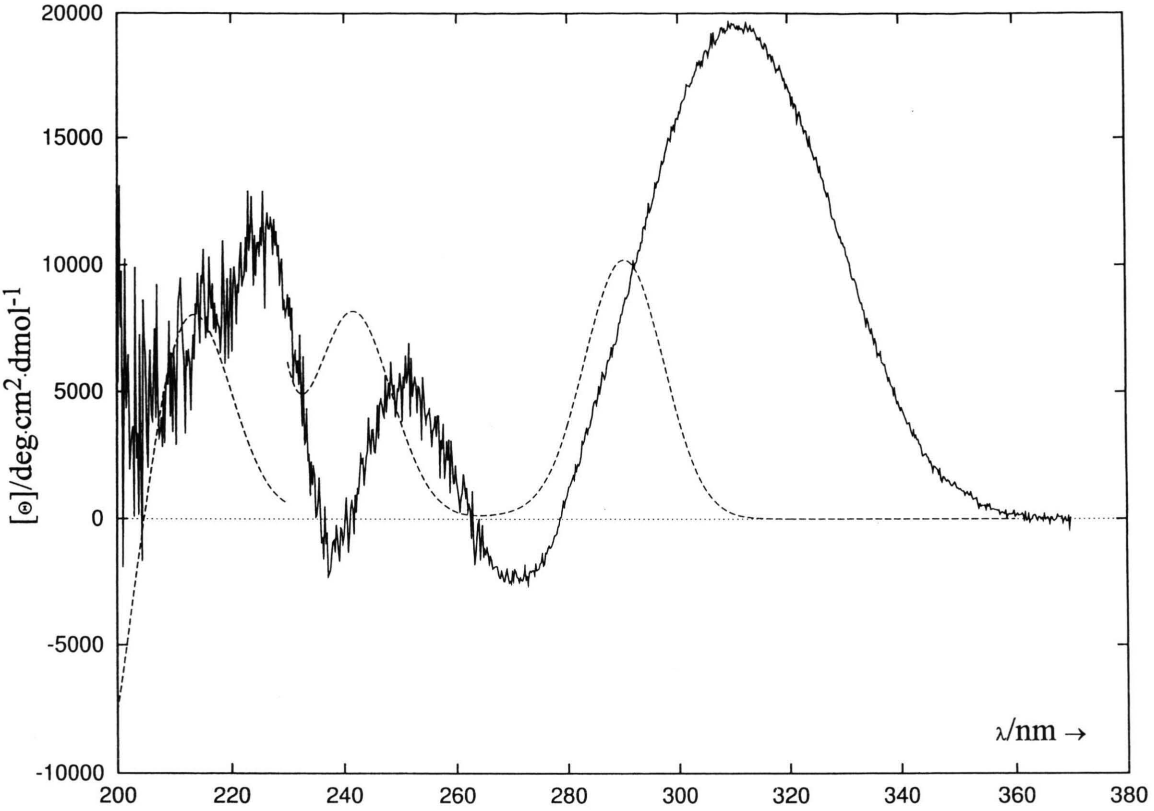

Fig. 2. Experimental (—) and Boltzmann-weighted calculated (- - -) CD spectrum of aldehyde ester **1**. Below 230 nm the calculated molar ellipticity ([$\Theta$]) was devided by ten.

approximation, where the loci and charges are obtained by a numerical method described in [12, 13]. An advantage of the matrix method is that it allows the use of experimentally determined transition energies instead of the corresponding calculated values whenever the latter are too poor. Thus, in the case of **1** the CNDO/2S method predicts the $n\pi^*$ transitions of those fragments which contain carbonyl groups (methyl acetate and acetaldehyde) at much too long wavelengths, while those of the other fragments (thiophenol and 1,2,3-trimethoxybenzene) are in reasonable agreement with the observed data. Consequently, we used the experimentally determined transition energies of the chromphores, which are listed in Table 2, instead of the corresponding calculated values.

Finally, rotational strengths of the ground state transitions were calculated by means of the origin-independent dipole velocity formalism and then multiplied with Gaussians (half bandwidth: 10nm over the entire considered range of wavelengths). Addition of these curves resulted in the total spectrum for each conformer. These spectra were then Boltzmann-weighted and superimposed to yield the total spectrum.

## 3. Results and Discussion

The calculated spectra of the four most stable conformers (**1a** - **1d**) together with the rotational strengths are shown in Figure 1.

The spectra of **1a** and **1b** are quite similar, and both are very different from those of **1c** and **1d**. Because of their large Boltzmann factors, however, the total spectrum in Fig. 2 is mainly determined by **1a** and **1b**. Comparing this total spectrum with the experimental one (Fig. 2), we assign the calculated bands at 212, 241 and 290 nm to those observed at 220, 250 and 310 nm.

The calculated intensities of the lower transitions at 212 and 241 nm are ten and two times higher than those of their observed counterparts, while the intensity of the calculated transition at 290 nm is underestimated by a factor of about one half. The band calculated at 290 nm is due to an $n\pi^*$ excitation of acetaldehyde, while the $L_a$ bands of thiophenole and trimethoxy benzene contribute significantly to the absorption at 241 nm. Finally, the band at 212 nm can be ascribed to an $n\pi^*$ transition of methylacetate and the *B* band of the trimethoxy benzene.

The weak negative absorptions observed at 240 and 270 nm are not reproduced by our calculations. Transitions which are due to the $L_b$ bands of the aromatics are calculated around 270 nm. The corresponding rotational strengths, however, have a positive sign. Since these transitions are very weak, it might be that the matrix method gives the wrong sign in these cases. No band in the calculated spectrum could be assigned to the negative absorption observed at 240 nm (cf. Figure 2). Missing of the weak negative bands at 240 nm might be due to the fact that the matrix method does not take into account charge transfer effects between the groups. Thus, it is also possible that the positive signs of the very weak rotational strengths of the transitions around 270 nm are calculated correctly but that they are overcompensated by the band of a charge transfer transition with a negative rotational strength.

Since the signs of the three most important bands in the experimentally determined and in the spectrum calculated for the *R* isomer correlate, the (*R*)-configuration of **1** as determined by X-ray structure analysis is confirmed.

This is another result in support of our claim that the combination of experimental and theoretical CD spectroscopy can be used efficiently to determine the absolute configuration of molecules.

## 4. Experimental

A solution of the aldehyde ester for CD spectroscopy was prepared at a concentration of 36 mg/l by dissolving a weighed sample in n-hexane. The CD measurements were carried out on an AVIV (Lakewood, NJ, USA) 62 DS spectrometer ($\lambda < 260$ nm) and a JASCO (Japan Spectroscopic Co., Ltd., Tokyo, Japan) J-600 spectropolarimeter ($\lambda > 260$nm), both calibrated according to Chen and Yang [19]. The spectral bandwidths and the pathlengths of the optical cells used were 2 nm/2 mm ($\lambda < 260$ nm) and 1 nm/10 mm ($\lambda > 260$nm), respectively. The temperature was 27 °C.

### *Acknowledgements*

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