Monatshefte für Chemie 134, 883–888 (2003)
DOI 10.1007/s00706-002-0554-z

**Monatshefte für Chemie**
**Chemical Monthly**
Printed in Austria

# On the Chemistry of the Resveratrol Diastereomers

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Received October 15, 2002; accepted November 7, 2002
Published online February 20, 2003 

**Summary.** The (*E*)- and (*Z*)-diastereomers of resveratrol were investigated with respect to their photochemical and thermal diastereomerization reactions. The free enthalpy difference between the two diastereomers was estimated to be in the order of common stilbenes, with the (*E*)-diastereomer more stable by about 11–14 kJ mol$^{-1}$. The *Arrhenius* activation barrier of about 280 kJ mol$^{-1}$ was found to be quite high and implies that thermal equilibration cannot account for the (*Z*)-diastereomer found in nature. A preparative access to the (*Z*)-diastereomer by photodiastereomerization is described. The $^{1}$H and $^{13}$C NMR spectra of the two diastereomers were assigned and their absorption spectra and fluorescence quantum yields of the neutral and monodeprotonated species were determined.

**Keywords.** Thermal diastereomerization; Photochemistry; Acidity; Fluorescence; Absorption.

## Introduction

Resveratrol (**1**) is a minor, but very important natural product found among others in grapevines and peanuts [1]. In recent years this phytoalexin solicited considerable attraction due to its cardioprotective and cancer chemopreventive properties [2]. Despite such prominent interest the fundamental chemical properties of this stilbenoid compound, which exists as the diastereomeric pair (*E*)-**1** and (*Z*)-**1** have been addressed only scarcely [3]. Therefore we now describe the thermal and photochemical diastereomerization reactions and selected physicochemical properties of the two pure diastereomers, data which are of fundamental importance for physiological and analytical studies. In addition, they could answer the question of provenience of (*Z*)-**1** in certain natural products.

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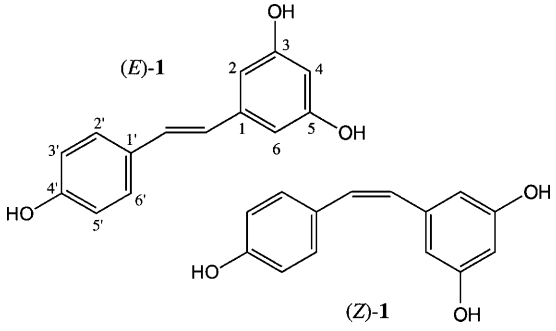


## Results and Discussion

### *Aspects of Preparation*

Due to its occurrence in natural materials in very minor amounts **1** has been the target of organic synthesis. The strategies either followed a *Wittig* route to build up the stilbene double bond [3a, 3b], a lithiation-condensation-dehydration cascade [3c], a phosphate variant [3d], a *Heck* reaction between an aryl and a styrene component [3e], or recently a solid-phase cross metathesis [3f]. By means of these reactions as well as by isolation from natural sources (*E*)-**1** has been the main product, and it is now commercially available. The (*Z*)-diastereomer was described to be accessible by photoisomerization [4]. It is present in very minor amounts in certain red wines only, but not in the grapes themselves [4b].

It should be mentioned that we investigated a different synthesis route to **1** trying to start with commercially available educts using *Seebach*'s Umpolung [5]. Whereas coupling of the dithiane, which was available in high yield from 3,5-dimethoxybenzaldehyde with 4-methoxybenzaldehyde, proceeded smoothly and in nearly quantitative yield, the desulfurization and subsequent dehydration of the product using a variety of standard methods [5, 6] failed completely.

### *Photochemical Aspects*

Interestingly enough, the photodiastereomerization yield of (*Z*)-**1** starting from (*E*)-**1** approached 90% without formation of byproducts. Because the irradiation source had higher emissions in the absorption region of the (*Z*)-diastereomer, and the (*Z*)-diastereomer has a lower extinction coefficient within the irradiation window, the (*E*)-diastereomer has a significantly higher (more than one order of magnitude) diastereomerization quantum yield than the (*Z*)-diastereomer. This high photoisomerization quantum yield makes this process feasible for the generation of (*Z*)-**1** in red wines. Although the photodiastereomerization yield was high the product could eventually be purified only by means of preparative HPLC (up to a purity of $\geq 98\%$).

It was interesting to note that the photoisomerization of (*Z*)-**1** in presence of diphenyl sulfide [7] proceeded sluggishly and rapidly produced colored byproducts. With regard to the very high thermal barrier (see below) this reaction could have been of interest in the case a chemical synthesis producing a mixture of the two diastereomers or mainly the (*Z*)-diastereomer if only the natural (*E*)-diastereomer would be needed.

*Thermal Diastereomerization*

Preliminary experiments showed that the most convenient temperature to study the thermal equilibration was in the 80°C region. Because isomerization is most important under physiological conditions, water was used as the solvent. The equilibrations were followed by means of UV measurements on thermostatted samples. Starting from both diastereomers of **1** the equilibrium mixture consisted of $>99\%$ of (*E*)-**1** and $<1\%$ (*Z*)-**1**. Accordingly, $\Delta G^\circ$ was estimated to be at least $11\,\mathrm{kJ\,mol^{-1}}$.

This result was corroborated by semiempirical calculations. Thus, AM1 calculations resulted in a more or less planar arrangement of (*E*)-**1** with $\Delta H_\mathrm{f} = -293\,\mathrm{kJ\,mol^{-1}}$. The (*Z*)-diastereomer was calculated twisted at the two aryl–ethylene bonds by about 38° with $\Delta H_\mathrm{f} = -279\,\mathrm{kJ\,mol^{-1}}$. Accordingly, the (*E*)-diastereomer of resveratrol was found to be more stable than the (*Z*)-diastereomer by $14\,\mathrm{kJ\,mol^{-1}}$ (gas phase), which is in the order of the relative stabilities of the diastereomers of stilbene ($17.6\,\mathrm{kJ\,mol^{-1}}$ [8]). Following the equilibration kinetics at 81, 83, and 85°C resulted in first order velocity constants of $9.0 \cdot 10^{-6}$, $1.7 \cdot 10^{-5}$, and $2.7 \cdot 10^{-5}\,\mathrm{s^{-1}}$, which allowed to estimate an *Arrhenius* activation energy of $280\,\mathrm{kJ\,mol^{-1}}$. Thus, the kinetic as well as thermodynamic stabilities of the diastereomers were found to be quite high. From these data it follows that the (*Z*)-diasteromer of resveratrol identified in certain wines [1] cannot originate from thermal equilibration, but could result from a photochemical reaction only.

*Acidity*

The electrometric titration of (*E*)-**1** with base revealed three significant steps corresponding to the mono-, di-, and tri-deprotonation of the system characterized by $pK_\mathrm{a}$ values of 9.3, 10.0, and 10.6. These values are within the range of common phenol acidity. The first deprotonation step might be assigned to OH-4′ because the charge of the corresponding phenolate ion can be delocalized over the whole molecule in this case only. Using a spectrophotometric titration, $pK_\mathrm{a}$ values could not be measured for the two diastereomers due to the strong absorption band overlap of the four coexisting species within such a closely spaced $pK_\mathrm{a}$ range. However, judged from the behavior of the UV absorption spectra upon variation of the *pH* the $pK_\mathrm{a}$ values for (*Z*)-**1** seem to be close to those of (*E*)-**1**. Due to these spectral overlaps it was also prohibitive to determine excited state acidities by means of a *Förster* cycle [9]. Only for the first deprotonation step of (*E*)-**1** an estimation of the $pK_\mathrm{a}^*$ of about 4 could be advanced. This acidification by about five orders of magnitude is similar to that observed for common phenols [9].

*Spectroscopic Properties*

The $^1$H and $^{13}$C spectra of the neutral diastereomers (*E*)- and (*Z*)-**1** in methanol-$d_4$ were assigned (Table 1) in a straightforward manner using shift arguments, coupling phenomena, and comparison with recently assigned *O*-methyl derivatives [10]. Using *DMSO*-$d_6$ as the solvent allowed also assignments of the three hydroxyl protons (Table 1). The significant low field shifts observed for the (*E*)-diastereomer protons nicely corroborated the more effective conjugation of the

**Table 1.** $^{1}H$ and $^{13}C$ chemical shifts ($\delta$/ppm) of (*E*)- and (*Z*)-**1** in $CD_3OD$ and *DMSO*-$d_6$ as solvents (25°C)

| Pos. | $CD_3OD$ | | | | *DMSO*-$d_6$ | |
|---|---|---|---|---|---|---|
| | (*E*)-**1** | | (*Z*)-**1** | | (*E*)-**1** | (*Z*)-**1** |
| | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{13}C$ | $^{1}H$ | $^{1}H$ |
| = 1 | 6.96[a] | 129.5 | 6.42[b] | 131.0 | 6.92 | 6.37 |
| = 1′ | 6.81[a] | 127.1 | 6.33[b] | 129.4 | 6.81 | 6.27 |
| 1 | – | 141.5 | – | 141.4 | – | – |
| 2,6 | 6.45 | 105.9 | 6.22 | 108.3 | 6.37 | 6.10 |
| 3,5 | – | 159.8 | – | 159.5 | 9.18 | 9.10 |
| 4 | 6.17 | 102.8 | 6.12 | 102.4 | 6.11 | 6.05 |
| 1′ | – | 130.6 | – | 130.0 | – | – |
| 2′,6′ | 7.36 | 129.0 | 7.10 | 131.6 | 7.39 | 7.07 |
| 3′,5′ | 6.77 | 116.6 | 6.63 | 116.0 | 6.74 | 6.62 |
| 4′ | – | 158.5 | – | 157.8 | 9.54 | 9.46 |

[a] $J = 16.6$ Hz; [b] $J = 12.4$ Hz

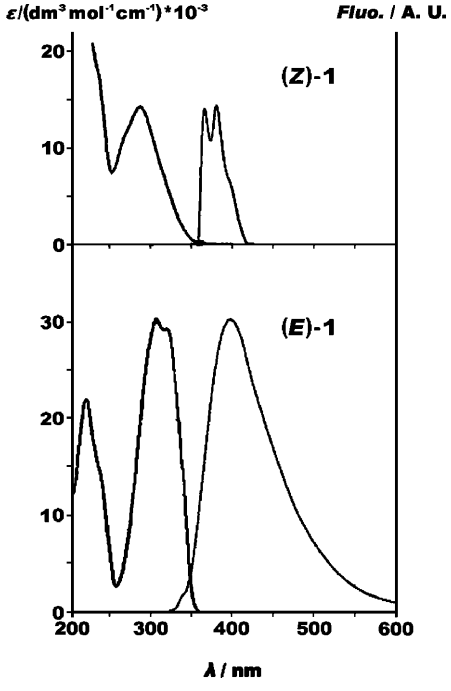


**Fig. 1.** UV and fluorescence spectra of (*E*)- and (*Z*)-**1** in methanol at ambient temperature

$\pi$-electrons in the (*E*)-diastereomer than in the (*Z*)-diastereomer as advanced from the semiempirical calculations.

The absorption and fluorescence curves of the diastereomers of **1** are displayed in Fig. 1. They are characterized by a strong hypsochromic (306 to 285 nm) and

hypochromic ($\varepsilon = 30400$ to $\varepsilon = 14200\,\mathrm{dm\,cm^{-1}\,mol^{-1}}$) shift of the (*Z*)-diastereomer and rather large *Stokes* shifts (99 and 81 nm for (*Z*)- and (*E*)-**1**) of the emission spectra. The fluorescence quantum yields of the two diastereomers ($\Phi_f(E) = 0.003$) and ($\Phi_f(Z) = 0.02$) differ by nearly one order of magnitude, which may be rationalized from the higher inflexibility of the sterically congested (*Z*)-diastereomer as derived from the semiempirical calculations mentioned above. Upon monodeprotonation a bathochromic shift of the main absorption band of (*E*)-**1** to 319 nm and of its fluorescence band to 450 nm was observed. The absorption of (*Z*)-**1** was shifted to 299 and its fluorescence to 402 nm. Such shifts are typical for the deprotonation of phenols [9]. Interestingly enough, the fluorescence quantum yields of the two monodeprotonated species became equal ($\Phi_f(E) = \Phi_f(Z) = 0.0015$).

## Experimental

(*E*)-Resveratrol ((*E*)-**1**) was of commercial origin (Sigma; $\geq 99\%$). Photodiastereomerizations were executed by means of a Hanau TQ 150 Z2 UV-lamp under an Ar atmosphere (MeOH or *DMSO* solution). For preparative HPLC separations a C8-reversed-phase column ($250 \times 4.6$ mm) on a Dionex P680/ASI100/PDA100 HPLC instrument applying a gradient from solvent A ($H_2O/MeCN = 95/5$, acidified with acetic acid to $pH = 3$) to B ($H_2O/MeCN = 5/95$), with a flow rate of $4\,\mathrm{cm^3\,min^{-1}}$, per cycle $200\,\mathrm{mm^3}$ of a $1.75\,\mathrm{g\,dm^{-3}}$ solution of **1** in solvent A were used. $^1H$ and $^{13}C$ NMR spectra were recorded by means of a Bruker Avance 200 MHz instrument. UV-spectra were measured on a Hewlett Packard HP 8453 and fluorescence spectra on a Hitachi F 4010 spectrometer. Fluorescence quantum yields were determined using quinine · HCl as the standard ($\Phi_f = 0.546$ [11]). Thermal isomerizations were followed using a Varian CARY 100 BIO instrument with a *Peltier* cell thermostat allowing to set temperatures within $\pm 0.01$°C. AM1 calculations [12a–12c] were executed using the program package MOPAC [12d] on the SGI Origin computer of the LIZENS of the Johannes Kepler University Linz.

## Acknowledgments

We are grateful to DI *B. Schwarzinger* and DI *B. Lackner* for discussions, HPLC settings, and recordings of spectra.

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