Determination of the Dimerization Equilibrium Constants of Omeprazole and *Pirkle*'s Alcohol through Optical-Rotation Measurements

by **Renato Baciocchi**

University of Rome 'Tor Vergata', Department of Chemical Science and Technology, via della Ricerca Scientifica 1, I-00133 Rome

and **Markus Juza** and **Jörg Classen**

CarboGen AG, Schachenallee 29, CH-5001 Aarau

and **Marco Mazzotti***[a]) and **Massimo Morbidelli**[b])

ETH Zurich, [a]) Institute of Process Engineering, ETH-Zentrum ML G25, Sonneggstrasse 3, CH-8092 Zurich, and [b]) Institute for Chemical and Bio-engineering
(e-mail: mazzotti@ipe.mavt.ethz.ch; tel.: +41-1-6322456(2486); fax: +41-1-6321141)

A new procedure to measure the equilibrium constants for the dimerization (homochiral and heterochiral) reactions of enantiomers in solution was applied to two different compounds, namely omeprazole and *Pirkle*'s alcohol, both in $CHCl_3$. This procedure is based on the measurement of the optical rotation of the solution as a function of its composition, which exhibits a nonlinear dependence on the enantiomer enrichment. Such nonlinearity depends on the extent of dimerization, and it is a strong effect in the case of omeprazole, whose equilibrium constants are 14.0 ± 3.5 l/mol and 25.2 ± 4.0 l/mol for the formation of homochiral and of heterochiral dimers, respectively. *Pirkle*'s alcohol exhibits a weaker effect that allows only to estimate the order of magnitude of these constants, *i.e.*, *ca.* 0.10 and 0.34 l/mol, respectively.

1. Introduction. – Association of enantiomers in solution is responsible for a number of remarkable phenomena, such as nonlinear behavior of optical rotation [1][2] and UV absorbance [3], nonlinear effects in asymmetric catalysis [4–7], as well as enantiomer enrichment through chromatography on achiral stationary phases [8–17]. Although, in solution, enantiomers and racemates of chiral compounds usually exhibit identical NMR spectra, small differences in the chemical shifts are sometimes observed (see [18] for an overview, as well as the ref. cit. therein). It is also known that nonracemic mixtures of enantiomers of compounds that strongly self-associate, *e.g.*, amino alcohols, amides, and carboxylic acids, can exhibit anisochrony, thus reflecting the enantiomer composition even in the absence of shift reagents [19]. Association is often limited to the formation of dimers that may take place through the formation of H-bonds between enantiomers. This is the case for the enantiomers of the chiral [1,1′-binaphthalene]-2,2′-diol (= binaphthol) and 1-(anthracen-9-yl)-2,2,2-trifluoroethanol (= *Pirkle*'s alcohol). In the case of the enantiomers of binaphthol in $CHCl_3$, we have recently been able, using an achiral chromatography column, to collect two fractions constituted of the pure enantiomer present in excess (reaching 100% e.e.) and of the racemic mixture, respectively [20]. In the case of *Pirkle*'s alcohol, the enantiomer enrichment of a nonracemic solution in hexane/CH_2Cl_2 was also achieved through achiral chromatography on a silica stationary phase [12].

The determination of the dimerization equilibrium constants of enantiomers is of interest for fundamental reasons as well as for applicative purposes, *e.g.*, in the context of preparative chromatography [15][21]. Until recently, only few papers have dealt with this problem. In particular, *Kitamura et al.* [5] measured the dimerization equilibrium constants of a methylzinc alkoxide by vapor-pressure osmometry, but, due to the difficulties of the technique, the authors wished that a more sensitive and accurate method might be developed. The association mode of ammonium and sulfonium sulfonates has been predicted by combined vapor-pressure osmometry and solubility measurements, but only qualitative results were achieved [22].

Recently, we developed a procedure for the determination of the dimerization equilibrium constants of enantiomers forming dimers [23]. This is based on using a polarimeter and analyzing its signal while accounting for the association behavior of the enantiomers in solution. Such a procedure was applied to the case of binaphthol, whose homochiral and heterochiral dimerization constants were measured, but we emphasized the general applicability of the proposed approach.

The aim of the present paper is to test the general validity of the proposed procedure for the determination of the dimerization equilibrium constants by optical-rotation measurements. This is achieved by applying this procedure to two organic compounds whose enantiomers are supposed to form dimers in solution, namely *Pirkle*'s alcohol and omeprazole (=5-methoxy-2-{[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]sulfinyl}-1*H*-benzimidazole; a commercial antiulcer agent) (see *Fig. 1*). A brief background section summarizes how to account for dimerization in analyzing polarimeter signals, and the experimental results of optical-rotation measurements are used to evaluate the dimerization equilibrium constants for the selected compounds.

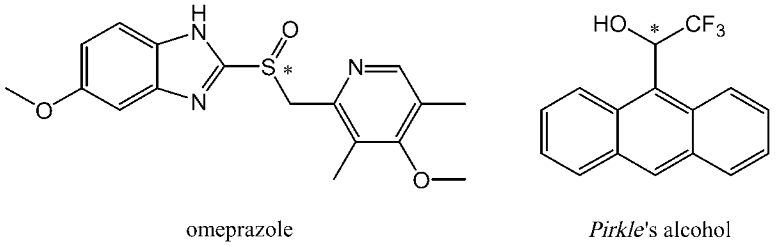

Fig. 1. *Structures of omeprazole and* Pirkle*'s alcohol*

2. Experimental. – 2.1. *Materials.* Racemic omeprazole was obtained from *Astra-Zeneca*, Mölndal, Sweden, and separated *via* enantioselective prep. HPLC. The chiral stationary phase *Chiralpak AS-V* was obtained as 20 μm bulk packing from *Chiral Technologies Europe*, Strassbourg, France. The purity of the obtained enantiomerically pure fractions was 99% ee (by HPLC). *Pirkle*'s alcohol was acquired from *Aldrich*, Buchs, Switzerland, as single enantiomers (98% ee (by HPLC)). The solvents used, *i.e.*, ^{i}PrOH/EtOH 70:30 (*v*/*v*) and $CHCl_3$, were reagent grade or better and obtained from a variety of sources.

2.2. *Methods.* Optical rotations: *Advanced* laser polarimeter (*PDR-Chiral, Inc.*, Palm Beach Gardens, Florida, USA), equipped with a 675-nm diode laser allowing for a detection limit of 25 μdeg; controlled temp. of 23°; flow-cell volume 103 μl and path length 5.17 cm. Anal. chromatography: *Gilson* (system (*Omnilab*, Mettmenstetten, Switzerland) consisting of a quaternary pump type *331/332*, sampling injector type *231*, a diode-array detector type *170*, and a syringe pump type *402*. Prep. HPLC: *Wellchrom* system from *Knauer* (Berlin, Germany) consisting of three *K-1800* pumps with 1000 ml/min pump heads, a HPLC box, a *K-2501* UV detector, and the above-mentioned laser polarimeter; *Merck* (Darmstadt, Germany) self-packed semi-prep.

column (230 mm × 48 mm i.d.); injected amount of omeprazole enantiomers in ^{i}PrOH/EtOH 7:3; *ca.* 120 mg; eluent flow rate 100 ml/min.

3. Background[1]). – 3.1. *Preamble.* The procedure for the determination of the dimerization equilibrium constants by optical-rotation measurements is based on combining the description of the dimerization process through an equation linking the instrument reading with the composition of the solution to be measured. This is shown in this section, summarizing results reported in our previous paper [23].

3.2. *Dimerization.* When two enantiomers **R** and **S** in solution undergo dimerization reactions, formation of both the homochiral dimers **RR** and **SS** and the heterochiral dimer **RS** takes place, according to *Eqns. 1–3.*

$$\mathbf{R} + \mathbf{R} \rightleftharpoons \mathbf{RR} \tag{1}$$

$$\mathbf{S} + \mathbf{S} \rightleftharpoons \mathbf{SS} \tag{2}$$

$$\mathbf{R} + \mathbf{S} \rightleftharpoons \mathbf{RS} \tag{3}$$

The couples constituted by the homochiral dimers **RR** and **SS** are also enantiomers, whereas those formed by the heterochiral dimer and one of the homochiral dimers, *i.e.*, **RR** and **RS** or **SS** and **RS**, are diastereoisomers. Due to symmetry, only the two reaction equilibrium constants, *i.e.*, K_{homo} and K_{hetero}, are needed to describe the reacting system. This implies that, assuming equilibrium of the dimerization reactions and ideal behavior of the liquid phase, the concentrations of the homochiral and heterochiral dimers can be written as $d_{\mathbf{RR}} = K_{\mathrm{homo}} m_{\mathbf{R}}^2$, $d_{\mathbf{SS}} = K_{\mathrm{homo}} m_{\mathbf{S}}^2$, and $d_{\mathbf{RS}} = K_{\mathrm{hetero}} m_{\mathbf{R}} m_{\mathbf{S}}$, where $m_{\mathbf{R}}$ and $m_{\mathbf{S}}$, and $d_{\mathbf{RR}}$, $d_{\mathbf{SS}}$, and $d_{\mathbf{RS}}$ represent actual monomer and dimer molar concentrations, respectively. Let us now consider the case of a solution of the **R** and **S** enantiomers, prepared at the molar concentrations r and s, or in other words, at total concentration $c = r + s$ and at a given enantiomer ratio $q = r/s$. The total concentration of the two enantiomers in solution is given by the material balances of *Eqns. 4* and *5*, which, upon application of the chemical equilibrium relationships represents a one-to-one mapping between overall concentrations r and s and the monomer concentrations $m_{\mathbf{R}}$ and $m_{\mathbf{S}}$. These can be inverted, resulting in only one pair of positive values $(m_{\mathbf{R}}, m_{\mathbf{S}})$, which can be written in the form of a function of the concentrations r and s, depending on the values of the two equilibrium constants as shown in *Eqns. 6* and *7.*

$$r = m_{\mathbf{R}} + 2K_{\mathrm{homo}} m_{\mathbf{R}}^2 + K_{\mathrm{hetero}} m_{\mathbf{R}} m_{\mathbf{S}} \tag{4}$$

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[1]) Notations and abbreviations: c = overall molar concentration $= r + s$ [M]; d_{ii} = molar concentration of dimers (ii = **RR**, **SS**, **RS**) [M]; K_r = dimerization equilibrium constant (r = homo, hetero) [l/mol]; m_i = molar concentration of enantiomers in monomeric form (i = **R**, **S**) [M]; q = nominal enantiomer ratio of **R** and **S** enantiomers $= r/s$; r = overall molar concentration of the **R** enantiomer [M]; s = overall molar concentration of the **S** enantiomer [M]; α = optical rotation (instrumental reading) [mV]; δ = polarimeter response coefficient for enantiomers in monomeric form [mV·l/mol]; μ = polarimeter response coefficient for homochiral dimers [mV·l/mol]; homo = homochiral dimerization; hetero = heterochiral dimerization; **R** = monomer (enantiomer); **RR** = dimer (enantiomer); **RS** = dimer; **S** = monomer (enantiomer); **SS** = dimer (enantiomer).

$$s = m_{\mathbf{S}} + 2K_{\text{homo}}m_{\mathbf{S}}^2 + K_{\text{hetero}}m_{\mathbf{R}}m_{\mathbf{S}} \tag{5}$$

$$m_{\mathbf{R}} = m_{\mathbf{R}}(r, s; K_{\text{homo}}, K_{\text{hetero}}) \tag{6}$$

$$m_{\mathbf{S}} = m_{\mathbf{S}}(r, s; K_{\text{homo}}, K_{\text{hetero}}) \tag{7}$$

Thus summarizing, five species are present in solution, namely the enantiomers **R** and **S** and the dimers **RR**, **SS**, and **RS**. However, thanks to the three dimerization equilibria, only two parameters are needed to characterize the composition of the solution; these can be either the two overall concentrations r and s, or the monomer concentrations $m_{\mathbf{R}}$ and $m_{\mathbf{S}}$, or alternatively also the two parameters c and q. The equations above allow us to obtain from one pair of independent variables all the others.

3.3. *Optical Rotation.* The measured optical rotation of the solution is a result of the combined effect of all optically active species present. In this case, these are the two monomeric enantiomers **R** and **S** and the two homochiral dimeric enantiomers **RR** and **SS**. The heterochiral dimer is not optically active and plays no role here. Each pair of enantiomers contributes to the optical rotation of the solution to an extent proportional to the difference between the concentration of the two enantiomers themselves. Therefore, since optical rotation is additive, its instrument reading is given by *Eqn. 8*, where the response parameters μ and δ for monomers and dimers, respectively, will in general be different, in principle also in their signs [2][7]. Of course the operating conditions of the polarimeter (see *Sect. 2.2*) are kept constant for all measurements.

$$\alpha = \mu(m_{\mathbf{R}} - m_{\mathbf{S}}) + \delta(d_{\mathbf{RR}} - d_{\mathbf{SS}}) \tag{8}$$

By substituting the chemical-equilibrium relationships, *Eqn. 8* can be rewritten in terms of the concentrations of the two enantiomers **R** and **S** as shown in *Eqn. 9*. Such a relationship cannot be cast in the form of a linear function of $(r - s)$, unless there is no dimerization, *i.e.* either for $K_{\text{homo}} = K_{\text{hetero}} = 0$ or at very low concentration, where the quadratic terms in *Eqn. 9* become negligible. By combining *Eqns. 6* and *7* with *Eqn. 9*, the optical rotation results to be a function of the nominal enantiomer concentrations r and s, and of the four parameters K_{homo}, K_{hereo}, μ, and δ (*Eqn. 10*).

$$\alpha = \mu(m_{\mathbf{R}} - m_{\mathbf{S}}) + \delta K_{\text{homo}}(m_{\mathbf{R}}^2 - m_{\mathbf{S}}^2) \tag{9}$$

$$\alpha = \alpha(r, s; K_{\text{homo}}, K_{\text{hetero}}, \mu, \delta). \tag{10}$$

3.4. *Parameter Estimation*. The equilibrium constants K_{homo} and K_{hetero}, as well as the response parameters μ and δ, can be determined by fitting optical-rotation data measured for different values of r and s, *i.e.*, different overall concentrations c and enantiomer ratios q, by using *Eqn. 10*. Following the procedure reported in detail elsewhere [23], the parameters in *Eqn. 10* are independently evaluated in three steps. *Step 1:* the response factor μ for monomers is determined by using only the optical-rotation data corresponding to very low concentration, where the relationship of optical rotation *vs.* the difference $(r - s)$ is still linear. *Step 2:* the homochiral dimerization constant K_{homo} and the dimer response factor δ are measured by using only the optical-rotation data of solutions of one pure enantiomer, either **R** or **S**. *Step 3:* in the last step of the procedure, optical-rotation data relevant to solutions containing both enantiomers are used, allowing to determine the best-fit value for the heterochiral dimerization constant K_{hetero}.

4. Results and Discussion[1]). – 4.1. *Omeprazole.* The results of optical-rotation measurements of omeprazole enantiomers in $CHCl_3$ are reported in *Fig. 2*. Four data sets were collected, corresponding to solutions of omeprazole in $CHCl_3$, each having a constant q value, namely 1.24, 2.00, 4.23, and ∞, and different total concentration c. It is worth pointing out that the four data sets belong to the same straight line only at very low concentrations, whereas, at higher concentration values, they lie on four different curves, showing a clear and distinct nonlinear behavior. This result provides evidence that dimerization of omeprazole enantiomers is taking place, since, in the opposite case, the optical rotation would be linearly dependent upon the enantiomer excess $(r-s)$ as

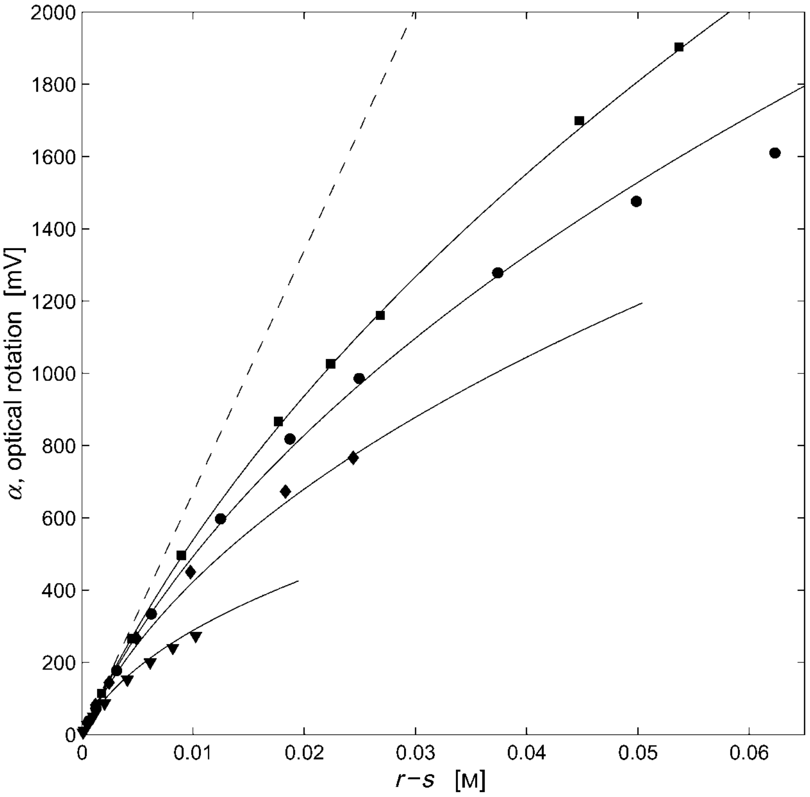

Fig. 2. *Optical rotation* vs. *difference of the nominal enantiomer concentrations* $(r-s)$ *for different mixtures of the omeprazole enantiomers in chloroform.* The solid curves are calculated with *Eqn. 10* and the parameter values $K_{\mathrm{homo}} = 14$ l/mol, $\mu = 67000$ mV · l/mol, $\delta = -5200$ mV · l/mol, and $K_{\mathrm{hetero}} = 25.2$ l/mol. The dashed line is the tangent to the experimental data in the origin. Enantiomer concentrations r and s are in the ranges 0.0005 – 0.081M and 0.0002 – 0.042M, resp. Symbols: ▮, $q = \infty$; •, $q = 4.23$; ◆, $q = 2.0$; ▼, $q = 1.24$.

expected for chiral compounds. It has been proposed that H-bonds are responsible for the formation of diastereomeric dimers of *N*-acetylvaline *tert*-butyl ester enantiomers in CCl_4 at – 20° [24]. A similar structure can be postulated for omeprazole enantiomers (see *Fig. 3*), assuming that the aprotic solvent $CHCl_3$ does not prevent the formation of H-bonds between the sulfoxide (proton acceptor) and the benzimidazole (proton donor) moieties.

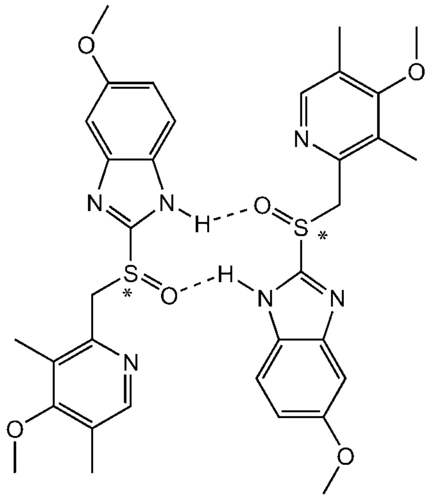

Fig. 3. *Proposed structure of the omeprazole dimers*

The observed optical-rotation behavior can be exploited for the evaluation of the dimerization equilibrium constants, by using the procedure summarized in *Sect. 3.4*. Following *Step 1*, the response factor of the monomer μ was found to be $\mu = 67000 \pm 15000$ mV · l/mol. In the absence of dimerization, this would result in a polarimetric signal corresponding to the dashed straight line in *Fig. 2*. *Step 2* of the procedure allowed us to evaluate the homochiral dimerization constant K_{homo} and the dimer-optical-rotation response factor δ. The results of the nonlinear regression are reported in *Fig. 4,a*, in terms of the sum of the squared errors (SSQ) between calculated and experimental optical-rotation values. The best fit values, $K_{\text{homo}} = 14.0 \pm 3.5$ l/mol and $\delta = -5200 \pm 2000$ mV · l/mol, were obtained. Finally, *Step 3* of the procedure was applied for the determination of the last parameter, *i.e.*, the heterochiral dimerization constant K_{hetero}. The results of the fitting, again given in terms of the SSQ values, reported in *Fig. 4,b*, provided the best-fit value of $K_{\text{hetero}} = 25.2 \pm 4.0$ l/mol. It is worth observing that the $K_{\text{hetero}}/K_{\text{homo}}$ ratio is close to the statistical ratio of 2, thus suggesting that there is only a small difference between the enthalpies of formation of the homochiral and of the heterochiral dimers [23].

4.2. Pirkle'*s Alcohol.* The results of optical-rotation measurements of *Pirkle*'s alcohol in $CHCl_3$, reported in *Fig. 5*, refer to three data sets, corresponding to solutions having constant *q* value, namely 2.00, 4.14, and ∞, and different total concentration *c*. By comparing the experimental data (symbols) in *Fig. 5* for this compound and in *Fig. 2* for omeprazole, it is rather evident that the response of the polarimeter is significantly

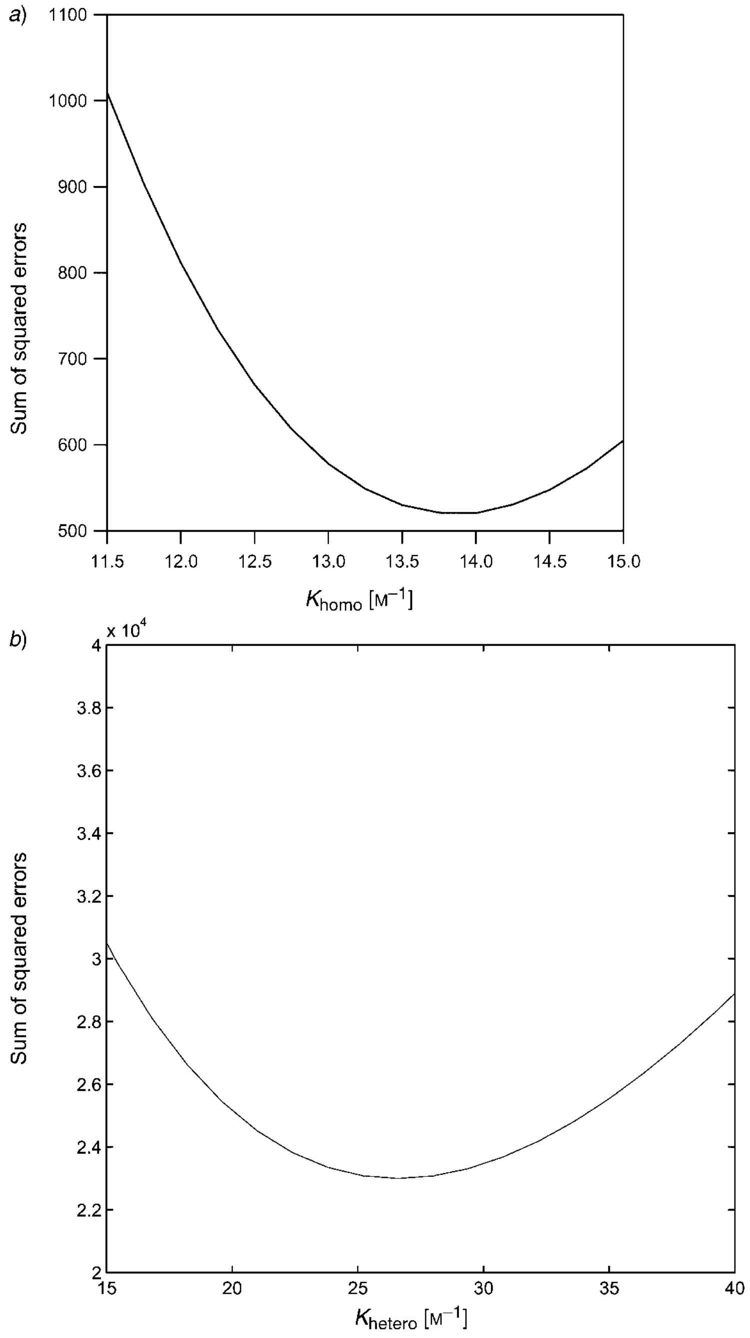

Fig. 4. *Estimation of the dimerization equilibrium constants of omeprazole* (sum of the squares of the absolute errors between exper. and calc. values of the optical rotation as a function of the relevant constant): a) *Estimation of* K_{homo} (*Step 2* of the procedure in *Sect. 3.4*; only data with $q = \infty$ are considered). b) *Estimation of* K_{hetero} (*Step 3* of the procedure in *Sect. 3.4*; all exper. data with $q < \infty$ are considered).

less nonlinear in the case of the *Pirkle*'s alcohol, even though, at higher concentrations, a clear, but weaker deviation from linearity was observed. The data sets belong to the same straight line at very low concentration. By applying the step-by-step procedure outlined in *Sect. 3.4*, the set of parameters used to draw the curves in *Fig. 5,a*, was obtained. However, in this case, such a determination could not be very accurate, and all parameters have rather large confidence limits. With reference to the figure, it is observed that the fitting is good only at $q = \infty$ but is rather poor for the other experimental conditions. The fitting procedure was repeated by considering the experimental points altogether, thus obtaining the new set of parameters used to draw the curves in *Fig. 5,b*, where the error between experimental points and model results is more evenly distributed. As far as the dimerization equilibrium constants are concerned, it is, however, worth observing that the quality of the fitting is rather insensitive to the specific values of K_{homo} and K_{hetero}, provided these are not larger than 0.10 and 0.34 l/mol, respectively, *i.e.* two orders of magnitude smaller than in the case of omeprazole. This indicates a rather weak association, as expected based on the weak nonlinearity of the optical-rotation measurements.

5. Conclusions. – Optical-rotation measurements were exploited to assess the occurrence of association of enantiomers in solution and to measure its extent, *i.e.*, the values of the equilibrium constants of the corresponding dimerization reactions. Two different situations were highlighted, both regarding the association of enantiomers in $CHCl_3$. The first case is that of omeprazole, where a strong nonlinear effect in optical rotation was observed, and a rather accurate estimate of the equilibrium constants could be made. This is similar to the binaphthol enantiomers in $CHCl_3$ [23]. In the case of *Pirkle*'s alcohol, on the contrary, the nonlinear effect was weaker, thus leading to a loss of accuracy in the estimation of the equilibrium constants, whose order of magnitude only (twice smaller than that of omeprazole) could be determined. The weak nonlinearity of the optical rotation might be due to a limited extent of dimerization or to a weak optical response of the monomers and of the dimers. Also in these cases, however, the precision of our approach is at least comparable to that based upon other methods proposed in the literature, characterized by uncertainties of one order of magnitude in the determination of dimerization constants [5][22]. Although the origin of self-association of homo- and heterochiral dimers of omeprazole and *Pirkle*'s alcohol cannot be elucidated conclusively with the presented data, it can, however, be conjectured that H-bonds are responsible for the dimer formation, as shown in *Fig. 3* in the case of omeprazole.

It is also worth noting that our results demonstrate how important it is to quantify the extent of dimerization reactions to avoid misinterpretation of optical-rotation measurements. A final remark concerns the thermodynamic significance of the dimerization equilibrium constants that were measured in this work, particularly those of omeprazole. Since the equations used are based on the assumption of ideal behavior of the solution, the effect of the solvent is embedded in the estimated values of K_{homo} and K_{hetero}. In fact, $CHCl_3$ that was used in this work is a solvent that allows for the formation of H-bonds between the solute molecules, contrary to more-polar solvents due to their solvation effects. To obtain values of the dimerization equilibrium constant devoid of solvent effects, one should include in the procedure a description of the

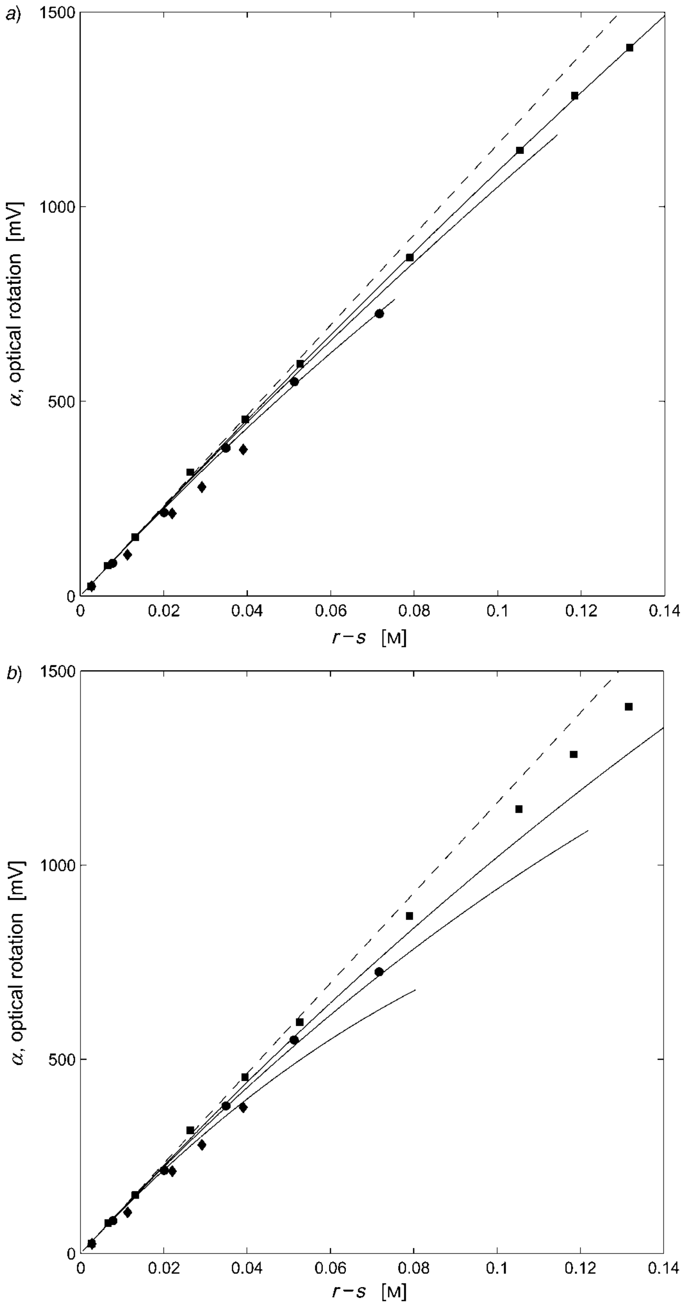

Fig. 5. *Optical rotation* vs. *difference of the nominal enantiomer concentrations* ($r-s$) *for different mixtures of* Pirkle'*s alcohol enantiomers in chloroform.* The solid curves are calculated with *Eqn. 10* and the following parameter values: *a*) $K_{\text{homo}} = 0.1$ l/mol, $\mu = 11600$ mV · l/mol, $\delta = -47000$ mV · l/mol and $K_{\text{hetero}} = 0.02$ l/mol; *b*) $K_{\text{homo}} = 0.1$ l/mol, $\mu = 11600$ mV · l/mol, $\delta = -122000$ mV · l/mol, and $K_{\text{hetero}} = 0.34$ l/mol. The dashed line is the tangent to the experimental data in the origin. Enantiomer concentrations r and s are in the ranges 0.0026 – 0.131M and 0.0023 – 0.034M, resp. Symbols: ■, $q = \infty$; ●, $q = 4.14$; ◆, $q = 2.0$.

nonideal behavior of the liquid phase if the solution is indeed nonideal. As such, the obtained values can be applied only to solutions of the enantiomers under examination in the same solvent used in the measurements. Such limitations apply also to the method based on vapor-pressure osmometry and proposed earlier [5].

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REFERENCES

[1] A. Horeau, *Tetrahedron Lett.* **1969**, *36*, 3121.

[2] A. Horeau, J. P. Guetté, *Tetrahedron* **1974**, *30*, 1923.

[3] J. Georges, *Spectrochim. Acta, Part A* **1995**, *51*, 985.

[4] C. Puchot, O. Samuel, E. Duñach, S. Zhao, C. Agami, H. B. Kagan, *J. Am. Chem. Soc.* **1986**, *108*, 2353.

[5] M. Kitamura, S. Suga, M. Niwa, R. Noyori, Z.-X. Zhai, H. Suga, *J. Phys. Chem.* **1994**, *98*, 12776.

[6] M. Kitamura, S. Suga, H. Oka, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 9800.

[7] C. Girard, H. B. Kagan, *Can. J. Chem.* **2000**, *78*, 816.

[8] K. C. Cundy, P. A. Crooks, *J. Chromatogr.* **1983**, *281*, 17.

[9] R. Charles, E. Gil-Av, *J. Chromatogr.* **1984**, *298*, 516.

[10] W.-L. Tsai, K. Hermann, E. Hug, B. Rohde, A. S. Dreiding, *Helv. Chim. Acta* **1985**, *68*, 2238.

[11] A. Dobashi, Y. Motoyama, K. Kinoshita, S. Hara, N. Fukasaku, *Anal. Chem.* **1987**, *59*, 2209.

[12] R. Matusch, C. Coors, *Angew. Chem., Int. Ed.* **1989**, *28*, 626.

[13] P. Diter, S. Taudien, O. Samuel, H. B. Kagan, *J. Org. Chem.* **1994**, *59*, 370.

[14] E. Loza, D. Lola, A. Kemme, J. Freimanis, *J. Chromatogr., A* **1995**, *708*, 231.

[15] R.-M. Nicoud, J.-N. Jaubert, I. Rupprecht, J. Kinkel, *Chirality* **1996**, *8*, 234.

[16] R. Stephani, V. Cesare, *J. Chromatogr., A* **1998**, *813*, 79.

[17] H. Takahata, S. Takahashi, S. Kouno, T. Momose, *J. Org. Chem.* **1998**, *63*, 2224.

[18] E. L. Eliel, S. H. Wilen, L. M. Mander, 'Stereochemistry of Organic Compounds', John Wiley, New York, 1994, p. 189 ff.

[19] M. I. Kabachnik, T. A. Mastryukova, E. I. Fedin, M. S. Vaisberg, L. L. Morozov, P. V. Petrovskii, A. E. Shipov, *Russ. Chem. Rev.* **1978**, *47*, 821.

[20] R. Baciocchi, G. Zenoni, M. Mazzotti, M. Morbidelli, *J. Chromatogr., A* **2002**, *944*, 225.

[21] M. Jung, V. Schurig, *J. Chromatogr.* **1992**, *605*, 161.

[22] R. U. Tamura, D. Fujimoto, Z. Lepp, K. Misaki, H. Miura, H. Takahashi, T. Ushio, T. Nakai, K. Hirotsu, *J. Am. Chem. Soc.* **2002**, *124*, 13139.

[23] R. Baciocchi, G. Zenoni, M. Valentini, M. Mazzotti, M. Morbidelli, *J. Phys. Chem., A* **2002**, *106*, 10461.

[24] A. Dobashi, N. Saito, Y. Motoyama, S. Hara, *J. Am. Chem. Soc.* **1986**, *108*, 307.

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