Investigation of tartaric acid amide formation by thermolysis of tartaric acids with alkylamines

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Abstract

N,*N*′-dialkyltartramides were obtained by conventional thermolysis at 200 °C without a solvent, of the *L*-, *D*- or *meso*-tartaric acids with butyl-, hexyl- and octylamine, respectively. The products proved in all cases to be mixtures of all the possible stereoisomers, in ratios that depended on the stereochemistry of the tartaric acid applied, retaining an excess of the configuration of the starting material. Isomerization of the initially formed diamide did not take place under the reaction conditions. Mechanistically the transformation was rationalized in terms of two competing pathways - the direct substitution of the alkylamine into the carboxylic acid group, - in competition with ketene formation and subsequent amide formation. As a method for stereoselective synthesis of optically active *N*,*N*′-dialkyltartramides, the method may be considered obsolete and of little practical value; however, it provided new insight into the mechanisms of amide formation.

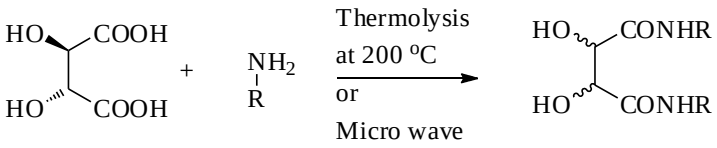
Keywords: Amphiphiles, functional surfactants, tartaric acids, tartramides, mechanisms, amide formation

Introduction

In an ongoing quest towards pseudo-biochemical[1] systems and associated reactivities, we are pursuing methods to create optically active amides with surfactant and supra-molecular properties. Initially, our target systems were derived from *N*,*N*′-dialkyltartramides. The amide moiety was chosen due to their robustness in aqueous media, for example relative to the corresponding esters.

Tartaric acids are inexpensive chiral pool compounds, useful for the construction of numeral chiral molecules. Currently we design and study supramolecular properties of new optically active amphiphiles, in which symmetric and unsymmetrically substituted tartaric diamides constitute the general base structures. Syntheses of amides usually call for multi-step

conversions, for example by the reaction of an appropriate amine with esters, anhydrides or acid halides. Amides may also be obtained by reacting carboxylic acids with amines in the presence of a diversity of activating reagents.[2,3] Direct formation of amides from acids and amines without activating auxiliaries, practical though rarely studied, are economically attractive alternative reactions. Several examples of such transformation have been reported, preferably of low molecular weight molecules, though mostly dating back to the mid-eighteenth hundreds.[4-16] Some of these methods appear quite versatile, although the method now is considered to be of lesser value.[17] Yet, more recent publications describe the successful synthesis of more complex molecules.[18-21] Formation of a number of tartramides by microwave irradiation of *L*-tartaric acid in the presence of the appropriate amines at 180 °C has been described.[22,23] In a recent publication our group reported that upon thermolysis or by microwave irradiation of mixtures of *L*-tartaric acid and hexylamine, *N*,*N′*-dihexyltartramide was formed in good yield, however, with partial racemization.[24]



Scheme 1. Tartaric diamides by the direct reaction of *L*-tartaric acids with amines.[22,24]

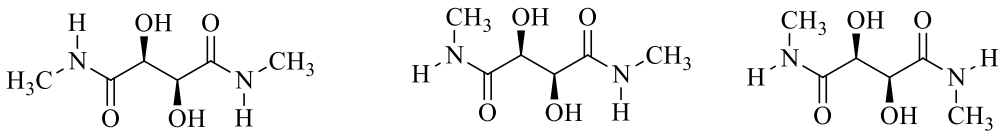
Product purity, including enantiomeric and diastereomeric purity, is a parameter of pivotal importance with respect to properties. So is also the case in relation to the properties of supramolecular systems. An abundance of reports illustrate the influence of enantio- and diastereomeric composition on supramolecular properties. Relevant to our work, should be mentioned work dealing with tartramonoamides reported earlier by Fuhrhop *et al.* These authors reported that enatiomerically pure tartramonoamides formed ultrathin fibers, while racemates appeared as planar platelets.[25,26]

Results and Discussion

For the applications of tartramides as structural entities in amphiphiles, control of purity was essential. To elucidate the detailed stereochemical outcome of the reaction for the direct synthesis of *N*,*N*-dialkyltartramides, Scheme 1, the transformation was scrutinized more closely. Tartramides prepared by reacting tartaric acid with amines were in all cases high temperature reactions, hence the potential targets of undesired side reactions. A general feature for all dialkyltartramides formed by this reaction was a number of signals in the NMR spectra, (proton and carbon) that could not be accounted for. Elemental analyses as well as MS data were in full agreement with the proposed structures.[22,24] Earlier reports dealing with the reaction shown in

Scheme 1[22,23] alleged the formation of enantiomerically pure diamides, however, without commeting upon the extra sets of NMR signals.

The extra sets of NMR-signals may be rationalized in terms of rotamers around the partial double C-N bond. To elucidate the conformational space, *N*,*N*′-dimethyltartramide as a model compound was examined by molecular modelling, using the *PCModel* package applying the MMX force field.[27] The *Z*,*Z*-conformer was predicted to be the more stable conformer, by as much as 6-7 kcal / mol, relative to the *Z*,*E*-conformer, which again was 5-6 kcal/mol more stable than the *E*,*E*-conformer. The rotational barrier for converting the *Z*,*Z*- into the *E*,*Z*-conformation was determined to 17-18 kcal/mol, comparable to the experimental rotational barrier measured to 18-21 kcal /mol for *N*-methyl-acetamide.[28]



Scheme 2. Conformations of *N*,*N*′-dimethyltartramide.

Variable temperature NMR experiments (temperature range 20–120 °C) with authentic (*R*,*R*)-*N*,*N*′-dioctyltartramide, **2c**, failed to demonstrate significant changes of chemical shifts - and coalescence was not observed. The collected evidence refutes the hypothesis that the multiplicity of signals is due to rotamers around the partial double C-N bond.

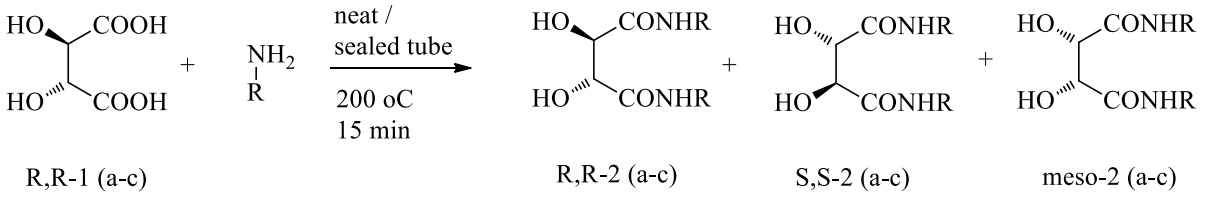
Thermolysis of tartaric acids with alkylamines.Reaction of *L*-tartaric acid, *R*,*R*-1, with alkylamines

Microwave irradiation in general function by creating superheated conditions. We instead choose to perform the reaction with conventional heating in sealed tubes at a slightly higher temperature (200 °C) compared to the 180 °C earlier used for the successful micro wave assisted reactions.[22,23] This also resembled the conditions described earlier.[18] Thus, (*R*,*R*)-tartaric acid, (*R*,*R*-**1**), was reacted at 200 °C for 15 min with alkylamines, used in 100 % excess. After acidic aqueous work-up (HCl) the products were isolated in 67-86 % yields, Scheme 3.

NMR and HLPC studies

The compositions of, for example, the crude product **2b**, from the reaction of *R*,*R*-**1** with hexylamine was studied by NMR and HPLC. There were strong indications that more than a single product was obtained. For example, in the NMR spectrum in $CDCl_3$ of the *N*,*N*′-dihexyltartramide product from *R*,*R*-**1**, and with the expected structure *R*,*R*-**2b**, two sets of signals were observed. The one set of signals were observed at 3.25 ppm (-C<u>H</u>$_2$-NH-), 4.23 ppm as a doublet (*J* = 7.5 Hz) (HO-C<u>H</u>-), 5.48 ppm as a doublet (*J* = 7.5 Hz) (-OH) and 7.07 (-NH-)

ppm of what in general constituted the main product. A minor product exhibited signals at 3.30 ppm (-C<u>H</u>$_2$-NH-), 4.00 ppm as a broad singlet (HO-C<u>H</u>-), 5.69 ppm as a broad singlet (-OH) and 7.07 ppm (-NH-) ppm. In DMSO the –NH- signals were observed at 7.58 ppm as a triplet with *J* = 6.0 Hz for the major and at 7.45 ppm as a triplet with *J* = 6.0 Hz for the minor product. That the two sets of signals correlated were indicated by comparing the integrations of the NMR signals. HH-COSY experiments further confirmed this assignment. The major product was assigned the structure *R*,*R*-**2b** and / or *S*,*S*-**2b**. The same characteristic sets of NMR signals were reported by other workers[22,23], however not commented upon.



R,R-1 (a-c) R,R-2 (a-c) S,S-2 (a-c) meso-2 (a-c)

R: a: n-butyl, 67 %, ratio (R,R-2a) : (S,S-2a) : (meso-2a) = 1 : 0.4 : 1.3
b: n-hexyl, 68 %, ratio (R,R-2b) : (S,S-2b) : (meso-2b) = 1 : 0.3 : 1.2
c: n-octyl, 86 %, ratio (R,R-2c) : (S,S-2c) : (meso-2c) = 1 : 0.4 : 1.3

Scheme 3. Thermolyses of *L*-tartaric acids with *n*-alkylamines.

The two sets of signals remained even after multiple crystallizations from acetonitrile, resulted in what appeared to be a pure product based on elemental analyses and mass spectrometric measurements. The variations in compositions of the crystallized products, were also, as indicated by the NMR measurements, associated with fluctuation of melting points, implying it to be mixtures of products.

After some effort, we succeeded in isolating the pure, main product **2b** by crystallization from a mixture of toluene:acetonitrile (1:1). The NMR spectrum of this product was in complete agreement with the one described above for the main product. Thermolysis of this product by reflux in xylene for 2 hours did not yield any signs of other products.

The minor product was eventually isolated from the recrystallization mother liquor and fully characterized. We reasoned this product to be the *meso*-*N*,*N*′-dihexyltartramide, *meso*-**2b**, based on the characteristic NMR data, and because isomerization was expected under the forcing reaction conditions. The structural assignment was further supported by comparison of the spectral data with those of an authentic sample, obtained by reacting dimethyl *meso*-tartrate with hexylamine in cold methanol. The results at this stage supported the view that the observed sets of NMR signals were due not to the presence of individual conformers, but caused by different compounds.

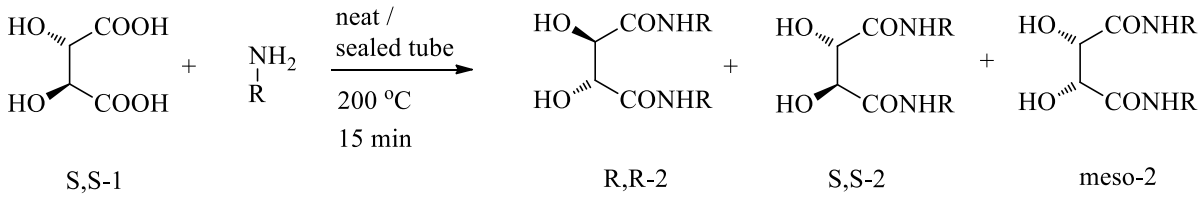
Did complete racemization take place under the reaction conditions? The optical rotation for crude product **2b** was measured to $[\alpha]_D^{20}$ = +29° (*c* 1.00, methanol) compared to specific rotation of pure, authentic *R*,*R*-**2b**, $[\alpha]_D^{20}$ = +93.2° (*c* 1.00, methanol), this clearly indicated that only

partial racemization had taken place in the course of the reaction. This was further confirmed by HPLC analyses using a chiral column. Thus, analysis of the crude *N*,*N*′-dihexyltartramide, **2b**, showed three products. By comparison with authentic samples they were identified as the two enantiomeric diamides *R*,*R*-**2b** and *S*,*S*-**2b** together with the *meso*-diamide, (*meso*-**2b**) in a 1:0.3:1.2 ratio. It could hence be concluded that extensive isomerizations had taken place, however not resulting in complete racemization.

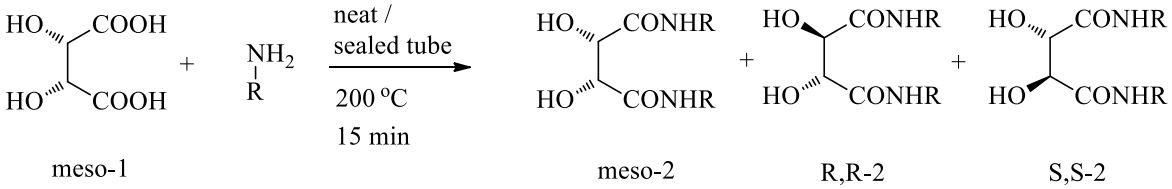
Similar results were obtained for the reaction of *R*,*R*-**1** with butylamine and octylamine resulting in products **2a** and **2c**. In both cases was obtained similar three-component mixtures as for the *N*,*N*′-dihexyltartramide system. The product ratios are shown in Scheme 3. It was noted that in all cases the *R*,*R*-**2** products constituted the major enantiomers.
Comparable results were obtained upon microwave irradiation.

Reaction of *D*-tartaric acid and *meso*-tartaric acid with alkylamines

In order to confirm the above reaction pattern and to obtain necessary reference materials, the analogous reactions were carried out with *D*-tartaric acid, Scheme 4. The NMR data were in agreement with those observed for the *L*-tartaric acid reactions. Chiral HPLC showed that in all cases the *meso*-products, (*meso*-**2a-c**), were formed together with enantiomers *R*,*R*-**2a-c** and *S*,*S*-**2a-c**, but now with products *S*,*S*-**2** as the major enantiomer, Scheme 4.



R: a: n-butyl, 74 %, ratio (R,R-2a) : (S,S-2a) : (meso-2a) = 1 : 1.7 : 1.8
b: n-hexyl, 62 %, ratio (R,R-2b) : (S,S-2b) :(meso-2b) = 1 : 1.8 : 2.7
c: n-octyl, 80 %, ratio (R,R-2c) : (S,S-2c) : (meso-2c) = 1 : 2.1 : 2.9



R: a: n-butyl, 69 %, ratio (R,R-2a) : (S,S-2a) : (meso-2a) = 1 : 1 : 1.3
b: n-hexyl, 72 %, ratio (R,R-2b) : (S,S-2b) :(meso-2b) = 1 : 1 : 2.5
c: n-octyl, 53 %, ratio (R,R-2c) : (S,S-2c) : (meso-2c) = 1 : 1 : 2.9

Scheme 4. Thermolysis of *D*-tartaric acid and *meso*-tartaric acid with alkylamines.

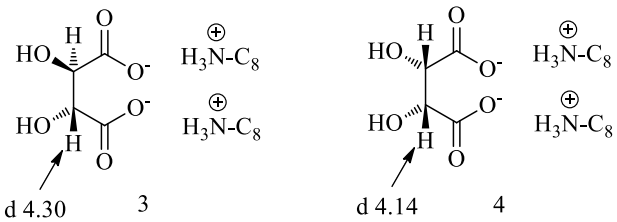
Finally, thermolyses were carried out with *meso*-tartaric acid, *meso*-**1**, Scheme 4. The commercial *meso*-tartaric acid contained ca. 5 % of the *syn*-tartaric acid as an impurity as shown by NMR analysis, with a characteristic main signal for *meso*-**1** at δ = 4.20 ppm together with a minor one at δ = 4.31 ppm due to *S,S*/*R,R*-**1**. We were not able to determine the composition of the byproduct by our chiral HPLC system. However, as the *meso*-tartaric acid in methanol did not display any optical rotation, the impurity presumably consisted of racemic *D*-/*L*-tartaric acid. The NMR spectra of the crude thermolysis mixtures showed that with all three alkyl amines, the *meso*-diamides were formed, with the characteristic NMR signals at δ = 4.01 and 5.69 ppm, together with the chiral diamides with NMR signals at δ = 4.23 and 5.48 ppm. Chiral HLPC analyses clearly showed that *meso*-diamides, *meso*-**2a-c**, were the main products together with the enantiomers, *R,R*-**2a-c** and *S,S*-**2a-c**. Within experimental error the ratios of products *R,R*-**2** and *S,S*-**2** were close to the expected 1:1. In all cases, isomer ratios changed somewhat, though not decisively, during the aqueous work-up, because the *meso*-diamides were surprisingly more soluble in water than the corresponding *R,R*- and *S,S*-diamides.

Thermolysis of alkylammonium tartrates

If pure dialkylammonium tartrate salts **3** and **4**, Scheme 5, were thermolyzed as melts under the same conditions described above, comparable product compositions were observed. Thus, thermolysis of the *R,R*-dioctylammonium *L*-tartrate salt resulted in a product containing *R,R*-**2c**/ *S,*S-**2c** and *meso*-**2c** in a 1.0 : 1.2 ratio. Mechanisti-cally this implied that an excess alkylamine was not essential to mediate the isomerization.

Mechanistic considerations

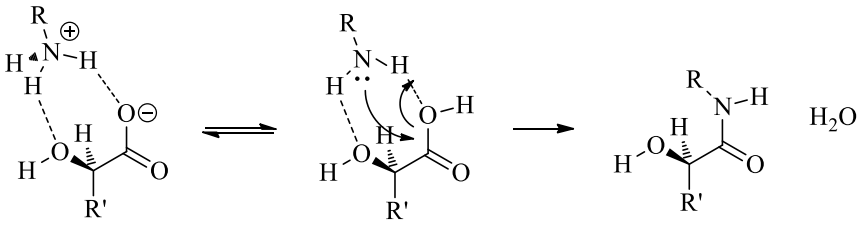
Mechanistically, formation of the isomers in the product mixture may be caused by isomerization of an initially diamide product, due to the presence of alkylamine bases. However, isomerization was not observed when authentic, pure *N,N′*-dioctyl-tartramide, *R,R*-**2c**, was heated with *N*-octylamine at 200 °C for 65 min. Similarly, when a solution of *R,R*-**2b** in THF was stirred with K-*tert*-butoxide at 50 °C for 60 min, no *meso*-**2b** was detected. A pre-reaction isomerization of tartaric acid was also unlikely, as partial conversion of *L*-tartaric acid in reactions with *N*-octylamine (200 °C, 6 min) revealed no signs of di-(*N*-butyl-ammonium) *meso*-tartrate in the NMR of the crude thermolysis product. Characteristic NMR signals in CD_3OD for the authentic *L*-tartrate alkylammonium salt, **3**, were observed at δ = 4.30 ppm and at δ = 4.14 ppm for the *meso*-salt, **4**, respectively, Scheme 5.



Scheme 5. Dialkylammonium tartrate salts **3** and **4**.

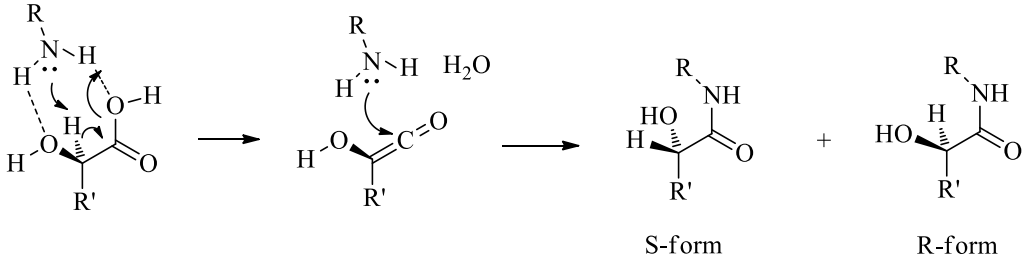
Comprehensive mechanisms for amide formation by thermolysis of acids with amines have so far not been presented in the literature. However, the combined evidence of the reactions described in this investigation, now make us propose a mechanistic scheme for the thermal conversion of ammonium tartrates into the corresponding amides.

The alkylammonium carboxylate group is in equilibrium with the free amine and carboxylic acid. The free amine may next function as either a nucleophiles or a base, thus leading to two competing reaction pathways. As a nucleophile the alkylamine attack the carboxylic acid carbonyl group, resulting in the direct formation of the amide together with one molecule of water, Scheme 6.



Scheme 6. Proposed mechanism for the direct amide formation.

Inspection of molecular models suggested that the amine through hydrogen bonding to the hydroxy and carboxylic acid groups, may be kept in close proximity of the carbonyl group, actually positioning the amino group near the Bürgi-Dunitz trajectory[30,31], allowing for the ready amide formation with simultaneous formation of one water molecule. It should be noted, that via this reaction pathway, isomerization about the chiral carbon will not take place. Thus, with this as the sole mechanism, just one diamide stereoisomer will be formed, with no changes of the absolute configurations at the stereogenic carbon atoms, for example *R*,*R*-**1** will give *R*,*R*-**2** only. A competing reaction route is launched, when the alkylamine instead functions as a base. The alkylamine, essentially from the same position as in the above transformation, may abstract the α-proton with simultaneous cleavage of water, resulting in the formation of a ketene intermediate, which upon addition of the alkylamine generates the amide group, Scheme 7. In an earlier investigation, we presented evidence that tartrates have the ability to generate ketene intermediates[32].



Scheme 7. Proposed mechanism for the amide formation *via* a ketene intermediate.

Through formation of the ketene, the chiral information associated with the α-carbon is lost, and as the alkylamine may attack from either side of the ketene moiety, products with both the *S*- and *R*-configurations will be produced, though not necessarily in equal amounts, as the reactions do take place in the chiral environments of the tartaric acids. Cyclic intermediates such as for example the anhydride or *N*-alkylimides are not unlikely, however, will not affect the final stereochemical outcome of the reaction.

Products formed from acid *R*,*R*-**1** through one direct- and one ketene reaction pathway, will consist of merely two product isomers, for example *R*,*R*-**2** and *R*,*S*-**2**.

If the ketene reaction represented the exclusive pathway for formation of both amide groups, the enantiomeric diamides were expected to be obtained in equal amounts. For example, from acid *R*,*R*-**1** the products *R*,*R*-**2** and *S*,*S*-**2** should be formed in 1:1 ratios.

This was, however, not observed. The enantiomers were formed in unequal amounts, and with an excess of the product enantiomer with the stereochemistry of the starting tartaric acid was observed. For example in the reactions of acid *R*,*R*-**1**, an excess of diamides *R*,*R*-**2** was formed relative to diamides *S*,*S*-**2**. The excess of diamides *R*,*R*-**2** was caused by the competing, direct amide formation. In conclusion, the observations can mechanistically best be rationalized in terms of the two competing reaction routes.

Interestingly we observed similar product formation when reacting diethyl *L*-tartrate with alkyl amines. When the reaction was carried out in methanol at 5 ^{o}C enantiomerically pure tartradiamide were formed. However, when the same reaction was performed in refluxing acetonitrile or toluene, the corresponding *meso*-product was also observed. Thus, we may have to reconsider the mechanisms for amide formation from the various acid derivatives.

We are currently conducting a more thorough mechanistic study of the direct amidation reactions.

Conclusions

The combined evidence of the work presented here, demonstrated that *N,N′*-dialkyltartramides were readily obtained by conventional thermolysis of tartaric acids with alkylamines at 200 ^{o}C. The resulting products were mixtures of all the possible stereoisomers, in ratios that depended on the stereochemistry of the tartaric acid starting material, However, an excess of the initial absolute configuration of the starting tartaric acid was retained in the product. Isomerization of the initially formed diamide did not take place under the reaction conditions. A mechanism for the transformation was proposed, which involved two competing pathways, - the direct substitution of the alkylamine with a carboxylic acid group, - in competition with ketene formation and subsequent amide formation. As a method for stereoselective synthesis of optically active *N,N′*-dialkyltartramides, the methods proved obsolete and of little practical value, however provided new insight into the mechanisms for amide formation.

Experimental Section

General. All chemicals and solvents applied were of synthesis quality unless otherwise stated and used as received without further purification. NMR-spectra were recorded on a Bruker Avance DPX300 or 400 instruments. TMS was used as an internal standard in samples dissolved in $CDCl_3$ or dioxane for samples dissolved in D_2O. IR spectra were obtained with a Thermo Nicolet Nexus FT-IR Spectrometer, and usually recorded using a Smart Endurance reflection cell. Mass spectra were obtained on a Thermo Quest MAT95X double focusing high resolution instrument using electron impact ionization using EI at 70 eV. Optical rotations were measured using a Perkin Elmer Model 341 Polarimeter. Chiral HPLC analyses were performed on a Agilent 1100 chro-matograph equipped with a Chiralcel OD column and a hexane / 2-propanol (95:5) as the eluent and the detector wavelength set at 210 nm. Melting points were determined using a Kofler bench (Wagner & Munz).

Thermolysis of tartaric acids with alkylamine. General procedure

In a sealed tube was placed a mixture of 1.50 g (10 mmol) of a tartaric acid together with an excess (40 mmol) of the appropriate alkylamine. The mixture was heated in an oil bath at 200 ^oC for 15 min. and then cooled to room temperature, upon which a solid was formed. The crude reaction product was subjected to NMR analysis, and then worked up adding 20 mL of water. The slurry of the products in water was acidified with hydrochloric acid, stirred for 5 min. and the products isolated by filtration, washed with water, and dried first in an air stream and finally in vacuo over phosphorous pentoxide. The isolated product was analyzed by NMR and chiral HPLC. The components of the products were identified by comparison of their spectroscopic and chromatographic properties with those of authentic samples. The results are shown in Schemes 2 and 3.

Measuring the optical rotation of the isolated products showed that the *ee* with respect to the desired configuration was between 23 and 35 %, *i.e.*, from *R,R*-**1** was obtained an excess of *R,R*-**2**.

Synthesis of authentic *N,N′*-dialkyltartramides from dimethyl tartrates and alkylamines. General procedure[33]

To a solution of 1.78 g (10 mmol) of a dimethyl tartrate (*L*, *D* or *meso*) in 20 mL of methanol was added 12 mmol of the appropriate alkyl amine. The resulting reaction mixture was stirred at 5 ^oC for 3 days. For the optically active diamides the precipitated crystalline product (the diamide) could be isolated by filtration, washing with small amounts of cold methanol, and then drying.

However, because the *meso*-diamides were remarkably soluble in hydroxylic solvent, this series of products were isolated by first evaporating the solvent (methanol) and next extracting the diamide with ether from an aqueous solution of the crude product.

(*R,R*)-*N,N′*-Dibutyltartramide (*R,R*-2a). 74% Yield, mp 196 ^oC. ^1H-NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, 6H), 1.34 (m, 4H), 1.51 (m, 4H), 3.26 (m, 4H), 4.23 (d, J = 7.5 Hz, , 2H), 5,49 (d, J

= 7.5 Hz, 2H), 7.08 (broad s, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 13.8, 20.1, 31.5, 38.9, 70.2, 174.1 ppm; IR (neat): 3316, 2958, 2931, 2873, 1637, 1536, 1460, 1430, 1375, 1311, 1278, 1249, 1128, 1152, 1088, 1058, 828, 723, 671 cm^{-1}; $[\alpha]_D^{20}$ = +112.0 º (*c* = 1.008, MeOH); HPLC: R_t = 12.6 min.

(*R,R*)-*N,N′*-dihexyltartramide (*R,R*-2b). 66% Yield, mp 184 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.90 (m, 6H), 1.33, (m, 12 H), 1.50 (m, 4H), 3.25 (m, 4H), 4.23 (d, *J* = 7.5 Hz, 2H), 5.48 (d, *J* = 7.5 Hz, 2H), 7.07 (broad s, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.2, 22.7, 26.6, 29.5, 31.6, 39.2, 70.1, 174.1 ppm; IR (neat): 3315, 2955, 2926, 2872, 2854, 1642, 1537, 1465, 1429, 1377, 1308, 1288, 1264, 1155, 1130, 1088, 1060, 827, 723, 673 cm^{-1}; $[\alpha]_D^{20}$ = +93.2 º (*c* = 1.006, MeOH); HPLC: R_t = 9.9 min.

(*R,R*)-*N,N′*-dioctyltartramide (*R,R*-2c). 82% Yield, mp.178ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.88 (m, 4H), 1.27 (m, 20H). 1.49 (m, 4H), 3.24 (m, 4H), 4.23 (d, *J* = 7.0 Hz, 2H), 5.48 (d, *J* = 7.0 Hz, 2H), 7.08 (broad s, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.2, 22.8, 26.9, 29.3, 29.4, 29.5, 32.0, 39.2, 70.1, 174.1 ppm; IR (neat): 3329, 3200, 2955, 2918, 2872, 2849, 1642, 1537, 1466, 1429, 1378, 1314, 1273, 1150, 1130, 1088, 1058, 827, 722, 673 cm^{-1}; $[\alpha]_D^{20}$ = +78.4 º (*c* = 0.500, MeOH); HPLC: R_t = 8.4 min.

(*S,S*)-*N,N′*-dibutyltartramide (*S,S*-2a). Exhibited similar spectroscopic properties as *R,R*-**2a**. $[\alpha]_D^{20}$ = -112.2 º (*c* = 1.0, MeOH); HPLC: R_t = 14.7 min.

(*S,S*)-*N,N′*-dihexyltartramide (*S,S*-2b). Exhibited similar spectroscopic properties as *R,R*-**2b**. $[\alpha]_D^{20}$ = -92.9 º (*c* = 1.0, MeOH); HPLC: R_t = 11.3 min.

(*S,S*)-*N,N′*-dioctyltartramide (*S,S*-2c). Exhibited similar spectroscopic properties as *R,R*-**2c**. $[\alpha]_D^{20}$ = - 77.8 º (*c* = 1.0, MeOH); HPLC: R_t = 9.7 min.

***Meso*-*N,N′*-dibutyltartramide (*meso*-2°).** 56% Yield, mp 150 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.92 (t, 6H), 1.37 (m, 4H), 1.53 (m, 4H), 3.29 (m, 4H), 4.01 (s, 2H), 5,69 (s, 2H), 7.06 (broad t, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 13.8, 20.2, 31.5, 39.0, 70.4, 173.1 ppm; IR (neat): 3347, 3257, 2953, 2930, 2869, 1638, 1564, 1438, 1350, 1254, 1228, 1195, 1149, 1094, 1064, 1028, 978, 737 cm^{-1}; HPLC: R_t = 18.5 min.

***Meso*-*N,N′*-dihexyltartramide (*meso*-2b).** 63% Yield. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.91, 1.34, (m, 12 H), 1.54 (m, 4H), 3.30 (m, 4H), 4.00 (s, 2H), 5.69 (s, 2H), 7.07 (broad s, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.2, 22.7, 26.7, 29.4, 31.6, 39.3, 70.3, 173.1 ppm; HPLC: R_t = 14.0 min.

***Meso*-*N,N′*-Dioctyltartramide (*meso*-2c).** 58% Yield, mp 131 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.88 (m, 6H), 1.28 (m, 10 H), 1.54 (m, 4H), 3.28 (m, 4H), 4.02 (s, 2H), 7.06 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.2, 22.8, 27.0, 29.3, 29.4, 29.5, 31.9, 39.3, 70.4, 173.1 ppm; IR (neat): 3269, 3203, 2955, 2916, 2848, 1637, 1567, 1464, 1378, 1294, 1268, 1253, 1229, 1213, 1186, 1151, 1093, 1071, 1016, 941, 723 cm^{-1}; HPLC: R_t = 12.0 min.

***Meso*-dimethyl tartrate** was prepared by reacting *meso*-tartaric acid in methanol with Amberlyst-15 as catalyst, according to a procedure reported in the literature[34]. The product exhibited the following spectroscopic properties: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 6H), 4.57 (s, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 53.1, 73.1, 171.6 ppm

Other reference compounds

***Meso*-tartaric acid.** ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 4.20 (s) ppm; (400 MHz, CD_3OD): δ = 4.49 (s) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 72.9, 172.6 ppm

L-Tartaric acid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 4.31 (s) ppm; (400 MHz, CD_3OD): 4.54 ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 72.2, 173.2 ppm.

Di-(*N*-octylammonium) *R,R*-tartrate (3). ^{1}H-NMR (400 MHz, CD_3OD): δ = 0.90 (m, 6H), 1.32, (m, 20 H), 1.65 (m, 4H), 2.90 (m, 4H), 4.30 (s, 2H) ppm.

Di-(*N*-octylammonium) *meso*-tartrate (3). ^{1}H-NMR (400 MHz, CD_3OD): δ = 0.91 (m, &H), 1.34, (m, 20 H), 1.64 (m, 4H), 2.90 (m, 4H), 4.14 (s, 2H) ppm.

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References and Notes

1. The investigation described here is part of our venture into the emerging field we have coined *pseudo-biochemistry.* This involve systems and transformations that in concepts, structures, mechanisms and functions may resemble those found in known biologic systems, however do not replicate known biologic or biochemical systems. This work involve the construction of compounds, interacting system and supramolecular entities that in concept, structure, functions, behavior and reactivity may resemble biologic systems, including chemical trans-formation, synthesis of components, energy conversions, eventually self-replication, that do not occur in the known nature and are not based on known biochemical systems. In a way, one may argue, pseudo-biochemistry creates and studies a new nature.
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