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Factors Affecting Conformation of (*R,R*)-Tartaric Acid Ester, Amide and Nitrile Derivatives. X-Ray Diffraction, Circular Dichroism, Nuclear Magnetic Resonance and Ab Initio Studies

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Abstract: Derivatives **2a-15a** of (*R,R*)-tartaric acid (**1a**) with all combinations of methyl ester, amide, *N*-methylamide and *N,N*-dimethylamide groups, as well as the corresponding *O,O'*-dibenzoyl derivatives **1b-15b** and nitriles **16-18** have been synthesized. Their conformations have been studied by the NMR and CD methods in solution as well as by X-ray diffraction in the crystalline state. The preference for planar, *T* conformation of the four carbon chain is observed under conditions restricting the α-hydroxyacid, ester or amide group to be nearly planar, this conformation being stabilized by intramolecular hydrogen bonds of the S(5) motif and the electrostatic CO/C(β)H and CN/C(β)H coplanar bond interactions. The C=O/C(α)-O bond system tends to be either synplanar (ester, acid), or antiplanar (ester, primary and secondary amide). *Ab initio* calculations allowed to demonstrate that for the isolated molecules of diamides **10a** and **15a** there is strong preference for gauche $G^+(a,a)$ conformers, the driving force being the formation of the hydrogen bonded six-membered cycles of the S(6) motif joining the OH and C=O groups from two different halves of the molecule. The results compare favourably with the experimental values derived from NMR spectra of **15a** in nonpolar solvent. In the absence of intramolecular hydrogen bonding the *N,N*-dimethylamide group is better accomodated in a gauche G^- conformer. This releases the nonbonded interaction due to the amide methyl group *anti* to the carbonyl group. © 1997 Elsevier Science Ltd.

INTRODUCTION

Optically active tartaric acid holds a central position in the history of stereochemistry, ever since Pasteur's landmark experiment demonstrated the existence of enantiomers of the acid, in the form of a readily separable conglomerate of its sodium ammonium tetrahydrate salt.[1]

Absolute configuration of (+)-tartaric acid has been assigned by Bijvoet et al. in another milestone experiment in which anomalous scattering of zirconium K_α X-rays by sodium rubidium tartrate was analysed.[2] This result made it possible for the first time to actually determine the sense of chirality of all compounds chemically correlated to (+)-tartaric acid. Quite recently, with the rapid development and expansion of methods of asymmetric synthesis, derivatives of optically active tartaric acids have found applications as chiral auxiliaries in several important procedures, such as Sharpless epoxidation,[3] Rousch allylboration[4] and Yamamoto aldol,[5] ene[6] and Diels-Alder[7] reactions, as well as enantioselective carbon-carbon bond formation via allenyl boronic esters.[8] Toda[9] used the *N,N,N',N',O,O'*-hexamethyl derivative of tartramide for resolution of racemates via

enantioselective complexation. Tartaric acid, *O,O'*-dibenzoyltartaric acid and its recently introduced mono(*N,N*-dimethylamide) are widely used as resolving agents for chiral amines.[10]

Structural data on tartaric acid[11] and its salts,[12,13,14] derived from the analysis of X-ray and neutron diffraction data, are abundant. The crystal structure of (+)-tartaric acid was first solved by Stern and Beevers in 1950,[11a] subsequently determined using neutron diffraction by Okaya, Stemple and Kay[11b] and recently refined at various temperatures by Albertsson, Oskarsson and Stahl.[11]

The most general description of the tartrate molecular geometry in the acid and its salts is a planar zig-zag conformation[15] (Figure 1, *T*, R = H, X = OH or O^-) with C(1)-C(2)-C(3)-C(4) torsional angle deviating less than 10° from the ideal value 180°. In the majority of cases of metal chelates, where the tartrate ion is a ligand, the five-atom unit -O(O=)C-C-O-, is nearly planar.[12,13] However, examples of significant deviations from planarity are known; in calcium tartrate tetrahydrate the O-C(1)-C(2)-O torsional angle is 22°.[12i] Examples of this type are also found among the salts of tartaric acid with amines.[14a,o,p] In addition, the tartrate moiety may show considerable asymmetry in the crystal, with the two halves of the molecule having a different shape, e. g. in (*R,R*)-tartaric acid esters.[16]

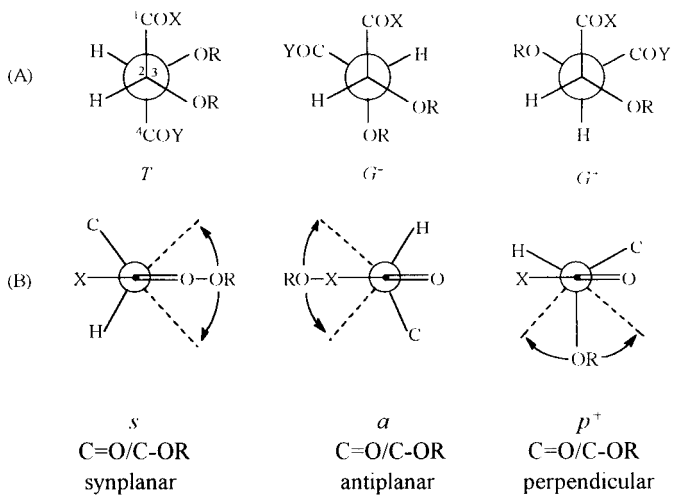


Figure 1. The three principal staggered conformations of (*R,R*)-tartaric acid derivatives around the C*-C* bond (A) and the three principal C-OR/C=O rotamers around the C-C* bond (B).

The planar *T* conformation of tartaric acid is also maintained in solution, as suggested by an early explanation of the optical rotation[17] and more recently by experimental and theoretical vibrational Raman optical activity (ROA) studies.[18] Supporting evidence comes from the early *ab initio* calculations, which predict that *T* conformer with intramolecular hydrogen bonding between the OH and C=O group attached to the same chiral carbon atom is energetically favoured.[19a] Energy minimization calculations and molecular dynamics simulation using two different force fields (MM2 and GROMOS) also point to pronounced preference for the *T* conformer.[19b] Moreover, the contribution of a planar *T* conformer of tartaric acid does not change much with pH, as demonstrated by measurement of $^2J_{C,H}$, $^3J_{H,H}$ and $^3J_{C,H}$ coupling constants in D_2O solution.[20]

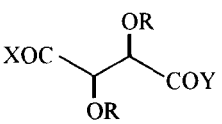
By comparison, structural data on covalent derivatives of tartaric acid appear surprisingly scarce. The available X-ray diffraction analysis data for *O*-(2,6-dimethoxybenzoyl)-tartaric acid[21] and salts of 2-*O*-benzoyltartaric acid[22] and 2,3-*O,O'*-dibenzoyltartaric acid[23] demonstrate that in the crystal these molecules assume *T* conformation. The same is true for tartaric acid *N,N'*-diisopropyldiamide[24] and even for the tartrate molecules incorporated into the macrocyclic [18]-crown-6 molecules.[25] Strong predominance of the *T*-

conformer in solution is observed for dialkyl tartrates from the vibrational circular dichroism (VCD) of C-O stretching vibrations.[19,26] Negative exciton Cotton effect of *O,O'*-dibenzoyl derivative of diethyl (*R,R*)-tartrate in solution can be accounted for by the dominance of the *T*-conformer.[27]

While these results may suggest that the tendency for favouring the *T* conformer is preserved in all tartaric acid derivatives, this contention is not supported by recent studies. X-ray crystal structures of di-, tri- and tetrameric titanium catalysts for Sharpless asymmetric epoxidation reveal either *T* or G^- conformers of dialkyl tartrate ligands.[28] A similar bent conformer of *O,O'*-dimethyl-*N,N,N',N'*-tetracyclohexyldiamide of tartaric acid was found in the lattice inclusion compound.[9] A conformer close to G^+ was found by the X-ray diffraction analysis of the monoester of *O,O'*-diacetyl-(*R,R*)-tartaric acid with (*S*)-timolol. Its dominance is apparently due to the intramolecular COOH···N hydrogen bond formation.[29] Our recent CD study of *O,O'*-dibenzoyl[27a] or *O,O'*-dicinnamoyl[30] derivatives of *N,N,N',N'*-tetraalkyldiamides of tartaric acid and X-ray diffraction data on *N,N,N',N'*-tetramethyldiamide of tartaric acid and its *O,O'*-dibenzoyl derivative[27a,31] demonstrated that the G^- conformer of uncomplexed molecule is energetically favoured both in polar solution and in the crystal.

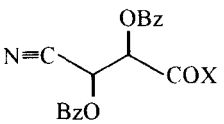
This has prompted us to study the conformation of tartrates and tartramides in solution and in the solid state systematically. We report here the synthesis of all, symmetric and unsymmetric, derivatives of (+)-tartaric acid (**1a**) bearing the methyl ester, amide, *N*-methylamide and *N,N*-dimethylamide groups (compounds **2a-15a**) as well as their *O,O'*-dibenzoyl derivatives **1b-15b**. In addition mononitriles **16-18** have been prepared (Chart 1). The conformations of these derivatives were characterized by means of the NMR and CD spectra. To the knowledge of these authors molecular orbital theory has not yet been extensively applied to tartaric acid derivatives. We were therefore encouraged to apply the *ab initio* and semiempirical methods to selected tartaric acid derivatives. Furthermore, X-ray structural determinations of tartaric acid derivatives were performed to get a detailed insight in the conformation and association mode of the molecules in the crystal.

Chart 1



1a,b - 15a,b

a, R = H; **b**, R = Bz



16 - 18

	X	Y		X	Y
1	OH	OH	**9**	OMe	NMe_2
2	OH	OMe	**10**	NH_2	NH_2
3	OH	NH_2	**11**	NH_2	NHMe
4	OH	NHMe	**12**	NH_2	NMe_2
5	OH	NMe_2	**13**	NHMe	NHMe
6	OMe	OMe	**14**	NHMe	NMe_2
7	OMe	NH_2	**15**	NMe_2	NMe_2
8	OMe	NHMe			

16	X = OMe
17	X = NHMe
18	X = NMe_2

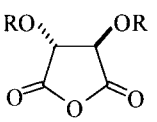
Synthesis.

Synthesis of **2a-15a**, **1b-15b** and **16-18** is summarized in Chart 2. All of these compounds have been prepared from commercial (+)-tartaric acid (**1a**) or its dimethyl ester **6a**. Other derivatives of **1a** used in the synthesis include cyclic anhydrides **19** and **20**, diester **21** and imide **22**.

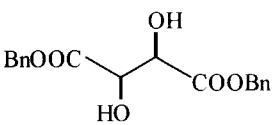
Chart 2

1a	a	**2a**	**20**	k	**1b**	**7a**	l	**16**
10a	b	**3a**	**20**	a	**2b**	**11a**	l	**17**
19	c,d	**4a**	**20**	h	**3b**	**12a**	l	**18**
21	e,f	**5a**	**20**	c	**4b**			
1a	g	**6a**	**20**	e	**5b**			
6a	h	**7a**	**6a**	l	**6b**			
4a	i	**8a**	**3b**	i	**7b**			
6a	e	**9a**	**4b**	i	**8b**			
19	e,i,j	**9a**	**5b**	i	**9b**			
6a	h	**10a**	**10a**	m	**10b**			
7a	c	**11a**	**4b**	n	**1b**			
7a	e	**12a**	**5b**	n	**12b**			
6a	c	**13a**	**13a**	m	**13b**			
22	e	**14a**	**5b**	o	**14b**			
6a	e	**15a**	**15a**	l	**15b**			

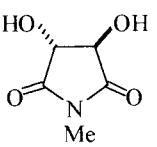
(a) MeOH, (b) aq. NaOH, (c) $MeNH_2$, (d) Dowex 50 W, (e) Me_2NH, (f) H_2/Pd-C, (g) $MeOH/H_2SO_4$, (h) NH_3, (i) CH_2N_2, (j) MeOH/KCN, (k) H_2O, (l) BzCl/py, (m) BzCl/NaOH, (n) NH_3/DCC, (o) $MeNH_2$/DCC



19 R = Ac
20 R = Bz



21



22

X-Ray Data Collection, Solution and Refinement of the Structures.[32]

The reflection intensities were measured on a four-circle *KM-4* (*KUMA Diffraction*)[33] diffractometer, except for **12a** the crystal of which was mounted on a Syntex $P2_1$ diffractometer.[34] Both diffractometers were equipped with graphite monochromator. Mo Kα radiation was used for compounds **9a** and **12a**, and Cu Kα radiation for compounds **10a** and **13a**. The measurements were performed at room temperature with the exception of **9a** which was measured at 150K.[35] The cell constants and the orientation matrix were obtained from a least-squares fit of at least 15 centred reflections. The reflections were measured using ω-2θ scan technique with the exception of **13a** for which ω-scan was applied. Variable scan rate was applied, and a scan range in ω was from 1.0° to 1.2°. Background measurements were estimated from 64- to 96-step profile. Reflections for which [$F>4\sigma(F)$] were considered as observed. The intensities were corrected for Lorentz and polarization effects, absorption corrections were not applied. The structures were solved by direct methods with

SHELXS-86[36] and refined with SHELXL-93.[37] Heavy atoms (C, O, N) were refined anisotropically. The positions of the H-atoms attached to the C- and N-atoms were calculated and refined using a riding model with a common isotropic temperature factor. The positions of the OH H-atoms were determined from difference Fourier maps and refined isotropically. The function minimized was $\Sigma w(|F_o|^2 - |F_c|^2)^2$ with $w=1/[\sigma^2(F_o^2)+(aP)^2+bP]$ where $P=(\max F_o^2+2F_c^2)/3$ and $\sigma(F_o)$ is the standard deviation of the observed amplitudes based on counting statistics: *a* varied from 0.05 to 0.18, and *b* varied from 0.00 to 0.55. Siemens Stereochemical Workstation was used to prepare drawings.[38]

Gas-Phase Computational Methods.

Molecular mechanics calculations were performed with a PCMODEL package based on the MMX force field[39] for symmetrical derivatives **6a**, **10a**, **13a** and **15a.** Minimum energy conformers were searched for each molecule with the use of dihedral driver with 10° step for rotation around the O=C-C*-O and C-C*-C*-C bonds. Starting geometry was 180° for the C-C*-C*-C angle and 0° for the O-C*-C=O angles. These searches were performed in the charge-charge interaction mode and in the hydrogen bonding mode.

Ab initio and semiempirical methods have been applied to study the diamide of tartaric acid **10a** and its tetramethyl analogue **15a**. Since each of these molecules has as many as five independently rotable bonds that are of crucial, conformational importance, a systematic scan of all possible conformations at the *ab initio* level is not feasible practically because of enormous demands made on computer resources. Therefore we decided to perform such a thorough search at the semiempirical level, employing MNDO (Modified Neglect of Diatomic Differential Overlap),[40] PM3 (Parametrized Model 3)[41] and AM1 (Austin Model 1)[42] methods that are based on the NDDO (Neglect of Diatomic Differential Overlap)[43] formalism. The semiempirical results subsequently served as initial data for *ab initio* calculations. These were carried out at the RHF level, at 3-21G (split valence)[44] and 6-31G* (polarized valence double ζ)[45] basis sets and with complete geometry optimization (standard, default algorithm). To perform all *ab initio* calculations we utilized GAMESS[46] program suite on Cray J916 and SGI Power Challenge L supercomputers in PCSS - Poznań, Poland. For the semiempirical part of the calculations we used the MOPAC package[47] running on PC 486.

Initial Z-matrices contained standard, average values of bond lengths and bond angles; dihedrals[48] were chosen in such a way that defines and retains the correct (*R,R*) diastereoisomer. There are five torsional angles that determine the entire conformation of the molecule. They are as follows: CC*C*C angle which determines the conformation of the carbon chain, two O=CC*O(H) angles which determine the mutual arrangement of amide and hydroxyl groups and, finally, two HOC*C* angles which determine the positions of hydroxyl hydrogen atoms with respect to the asymmetric carbon atoms. In order to perform a thorough search throughout the conformational possibilities one should define and completely optimize 432 initial geometries of each molecule, if, of course, one assumes that the number of angles of interest is 5 and the potential is 3- and 4-fold. In this case, however, we can reduce the number of initial geometries to be considered to 270 owing to the fact, that both molecules consist of two identical parts. The first stage of the study was based upon the rotation of one of the amide groups present in the molecules with respect to the carbon skeleton for each of the possible CC*C*C/HOC*C* settings. Those settings corresponded to the ones used in the study of 1,2-ethanediol[49] and its (*R,R*)-1,2-disubstituted analogues.[70] The amide group rotation calculations revealed 4 local energy minima. In the second stage O=CC*O(H) values, corresponding to those minima, were used in the calculations with complete geometry optimization of all combinations of torsional angles within the molecules. Initial structures for the *ab initio* calculations of **10a** were chosen from amongst the semiempirically optimized conformers, namely we have chosen the first ten geometries corresponding to the lowest energy values. For *ab initio* study of **15a**, nine conformers, that are shown in Fig. 3, have been considered. In both cases we have employed the RHF scheme at 3-21G and 6-31G* basis sets.

RESULTS

Circular Dichroism.

Since tartaric acid derivatives, with the exception of nitriles, contain the carbonyl group it was expected that the CD spectra within the range of the n-π* transition (200-230 nm)[50] should be sensitive to the changes in the immediate environment of this group, i.e. to the rotational isomerism involving the C(O)-C(α) bond. According to earlier studies homochiral lactones and lactams give the n-π* Cotton effects of the same sign.[51] Thus conformational preferences of the COX group in tartaric acids, esters and amides could be determined with the help of a sector rule, based on the quadrant rule originally developed for the amide group[52] (Figure 2a).

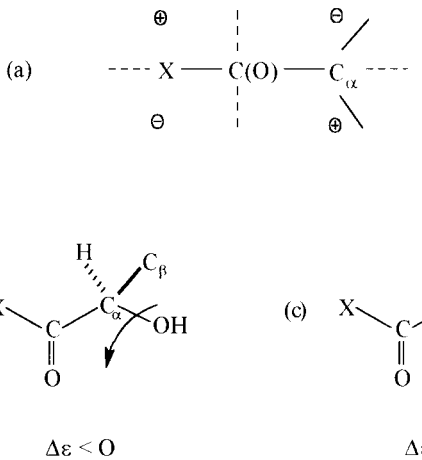


Figure 2. The sector rule for the sign of the n-π* Cotton effect of (*R,R*)-tartaric acids, esters and amides; (a) view along the axis of the O=C bond, (b) C=O/C-OH synplanar rotamer, (c) C=O/C-OH antiplanar rotamer.

According to this sector rule any substituent on C_α appearing in the upper right sector should give rise to a negative Cotton effect; the opposite sign is expected for a substituent in a lower right sector. Given the preference of the C*-OH bond for the coplanarity with the carboxylic group, two conformers of (*R,R*)-tartaric acid derivatives should be readily distinguished by the sign of the n-π* Cotton effect: the one with the C=O/C*-OH synplanar bonds should produce a negative Cotton effect (Figure 2b, M-helicity O=C-C(α)-C(β) bond system) while the one with the C=O/C*-OH antiplanar bonds should give a positive Cotton effect (Figure 2c, P-helicity O=C-C(α)-C(β) bond system). As shown in Table 1 the n-π* Cotton effects vary significantly. The symmetrical diacid **1a** and the diester **6a** give negative Cotton effects[53] while symmetrical diamides **10a** and **13a** are characterized by positive Cotton effects. The symmetrical tetramethyldiamide **15a** again gives a negative Cotton effect at 210 nm, with a smaller positive one at 233 nm. This allows us to conclude that synplanar rotamer in Fig. 2b is preferred for X = OH, OMe and NMe_2[54] while antiplanar rotamer, (Figure 2c) is more stable for X = NH_2 and NHMe. The unsymmetrical derivatives of tartaric acid show Cotton effects that can be attributed to a sum of Cotton effects due to the individual COX groups. These are obtained from the Cotton effects of symmetrical compounds, i.e. COOH, Δε -1.8; COOMe, Δε -2.65; $CONH_2$, Δε +1.6; CONHMe, Δε +2.05; $CONMe_2$, Δε -2.8. The additivity procedure gives results in satisfactory agreement with the experimental data (Table 1), within the limits of this semiquantitative approach.[55]

Table 1. The n-π* Cotton effects of (*R,R*)-tartaric acid derivatives **1a-15a** in water solution (c = 10^{-3}M) and the exciton Cotton effects of *O,O'*-dibenzoyl-(*R,R*)-tartaric acid derivatives **1b-15b** in dioxane (c=5•10^{-4}M)

compd	**1a**	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**	**8a**	**9a**	**10a**	**11a**	**12a**	**13a**	**14a**	**15a**
Δε	-3.6	-4.7	+0.6	+1.2	-6.9	-5.3	-0.7	-0.8	-5.5	+3.2	+4.0	+0.3	+4.1	+0.5	+0.3
(nm)	(215)	(213)	(216),	(210)	(207)	(215)	(217)	(225),	(212)	(213)	(210)	(228),	(210)	(224),	(223),
			-0.9					+1.3				-3.0		-1.2	-5.9
			(199)					(199)				(195)		(202)	(210)
compd	**1b**	**2b**	**3b**	**4b**	**5b**	**6b**	**7b**	**8b**	**9b**	**10b**	**11b**	**12b**	**13b**	**14b**	**15b**
Δε	-35.0	-33.0	-34.9	-35.0	-22.4	-32.4	-30.3	-29.9	-15.7	-30.8	-24.3	-10.6	-27.0	-2.8	+11.1
(nm)	(236)	(236)	(236),	(236)	(235)	(237)	(237),	(236),	(233)	(237),	(237),	(232),	(234)	(230)	(240),
			+3.5				+6.3	+4.5		+7.9	+6.5	+1.5			-10.7
			(220)				(218)	(219)		(220)	(219)	(218)			(226)

There is only one compound for which the calculated Δε value does not readily compare to the experimental one: **8a**, $\Delta\varepsilon_{calc.}$-0.6. The CD curve in this case is bisignate and the weighed value of Δε is +0.5. This discrepancy indicates the deviation of the ester or *N*-methylamide group from the preferred conformation discussed above

The above analysis of the CD data allowed the assignment of the preferred conformation around the C-C* bonds in tartaric acid derivatives in solution. In the rotational profile of (*R,R*)-tartaric acid derivatives (Figure 3) the columns visualize twofold rotation around C-C* bonds, whereas the rows represent rotations around the C*-C* bond.

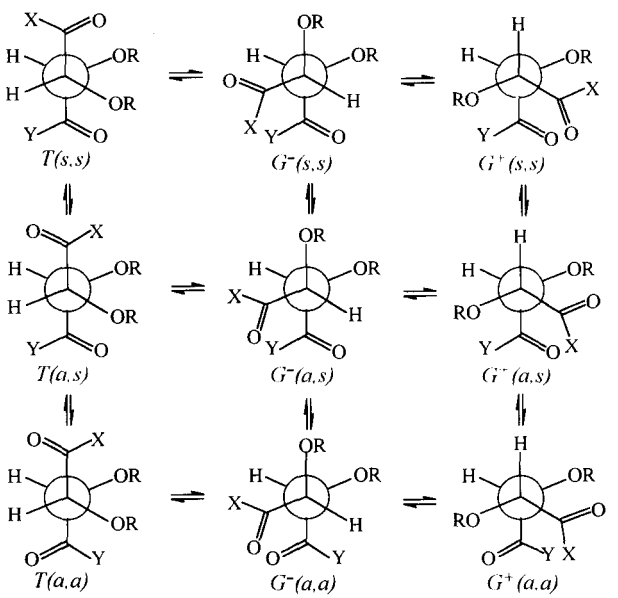


Figure 3. Rotational profile of (*R,R*)-tartaric acid derivatives (X = OH, OMe, NH_2, NHMe, NMe_2). The COX/COY trans conformers are in the first column, the C-H/C-H trans conformers are in the second column, and the C-OR/C-OR trans conformers are in the third column. The C-OR/C=O synplanar conformers are on the first row, the C-OR/C=O antiplanar conformers are on the third row, and the mixed (unsymmetrical) eclipsed conformers are on the second row. The C-OR/C=O perpendicular conformers are not included.

In order to obtain experimental data on the solution rotamers of tartaric acid derivatives around the C*-C* bond we have investigated the CD spectra of *O,O'*-dibenzoyl derivatives **1b-15b**. The method used is the dibenzoate chirality rule[56] which in turn is based on the exciton coupling mechanism.[57] This method has been recently applied to study conformation of acyclic 1,2-dibenzoate systems.[27] According to the concept of exciton interaction between the two benzoate chromophores, C*-C* rotamers depicted in the first column (*T*) should give *negative* exciton Cotton effect at around 230 nm, as the torsional angle O-C*-C*-O is negative and the two benzoate electric transition dipole moments system has negative chirality. On the other hand, C*-C* rotamers in the second column (G^-) should produce *positive* exciton Cotton effect at around 230 nm, while rotamers in the last column (G^+) do not contribute to the dibenzoate exciton Cotton effect (coplanar benzoate electric transition dipole moments).[58] The measured exciton Cotton effects at benzoate π–π^* charge transfer band in dioxane solution (Table 1) show negative sign (i.e. negative maximum at longer wavelengths[59]) for all dibenzoates, except **15b**. The amplitude of the exciton Cotton effect is large and negative (A = -27.0 to -38.7) for all derivatives, except *N,N*-dimethylamides **5b**, **9b**, **12b**, and **14b**. This means that in the absence of the *N,N*-dimethylamide group all other (*R,R*)-tartaric acid derivatives assume *T* conformation (Fig. 1) around the C*-C* bond. The *N,N,N',N'*-tetramethyldiamide **15b** exhibits positive exciton Cotton effects (A = +21.8) which is due to the conformer G^- (Figure 3).[27a,30] The reduced negative Cotton effect of other *N,N*-dimethylamides **5b**, **9b**, **12b** and **14b** can be interpreted as resulting from the contributions of both *T* and G^- conformers. If the contribution of G^+ conformer is neglected, one can estimate fractions of each *T* and G^- conformer from the CD data[60] (Table 2).

Table 2. Fraction of *T* and G^- conformers in dioxane solution as calculated from the CD data

	5b	**9b**	**12b**	**14b**	**18**
T	0.78	0.67	0.60	0.44	0.21
G^-	0.22	0.33	0.40	0.56	0.79

The mononitriles **16-18** also display dibenzoate exciton Cotton effects indicative of their conformation (Figure 4). Thus mononitriles **16**, **17** follow the trend for preferred rotamer *T* (negative exciton Cotton effect) while **18**, with *N,N*-dimethylamide group, exhibits positive exciton Cotton effect, characteristic of rotamer G^-.[61]

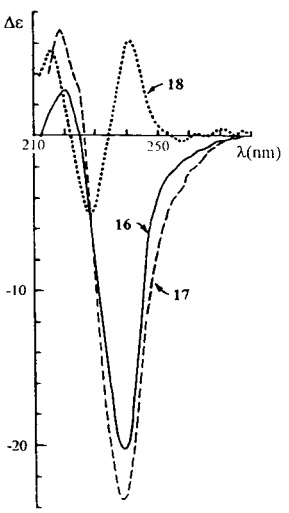


Figure 4. CD curves for *O,O'*-dibenzoyltartaronitriles **16-18** (solvent dioxane). Note positive exciton Cotton effect (A=+10.6) for **18** and a negative one for **16** (A=-23.4) and **17** (A=-29.1).

Nuclear Magnetic Resonance.

Although the CD measurements give insight into C*-C* rotational preferences of *O,O'*-dibenzoyl tartaric acid derivatives there remains a question of how well the solution conformation of these derivatives correlates with the conformation of derivatives having the free OH groups. NMR spectroscopy offers an independent way of assessing rotational equilibria. Table 3 shows $^{3}J_{H,H}$ coupling constants measured in methanol-d_4 solution, except for benzoylated derivatives, where solubility required the use of less polar solvents. Like **1a**, tartaric acid derivatives **2a-14a** show remarkable propensity toward the *T* conformer which is characterized by the low value (1.8-2.3 Hz) of $^{3}J_{H,H}$. For symmetry reasons $^{3}J_{H,H}$ could not be directly measured for **1a**, **6a**, **10a**, **13a** and the crucial derivative **15a** and the satellite band technique was applied.[62] It should be noted that in the case of two *N,N*-dimethylamides **5a** and **9a** $^{3}J_{H,H}$ has slightly higher value (2.6 Hz and 3.2 Hz) due to the increased contribution of the G^- conformer, but in the case of the two other *N,N*-dimethyldiamides **12a** and **14a** $^{3}J_{H,H}$ values remain typical of a *T* conformation. Since a low $^{3}J_{H,H}$ value is typical of two C*-C* conformers, i. e. *T* and G^+(Figure 1) we have used additional measurements of $^{2}J_{C^*,H}$ coupling constants to make correct conformational assignments. The $^{2}J_{C^*,H}$ coupling constant depends on the relative orientation of the O-C and C-H bond in an RO-C-C-H fragment: the larger the torsional angle RO-C-C-H the more positive is the value of $^{2}J_{C^*,H}$.[63,64] For a C*-OR bond antiperiplanar to a C-H bond in conformer *T* (Figure 1) there is a positive contribution of 5-8 Hz compared to a negative $^{2}J_{H,C}$ value of conformer G^- or G^+.[65] For tartrates and tartramides **1a-14a** in methanol solution the low $^{2}J_{C^*,H}$ value is indicative of *T* conformer (Table 3).

Table 3. $^{3}J_{H,H}$ and $^{2}J_{C^*,H}$ values for (*R,R*)-tartaric acid derivatives (solvent CD_3OD, c = 5 • 10^{-2} M, unless stated otherwise)

compd	**1a**	**2a**	**3a**	**4a**	**5a**	**6a**	**7a**	**8a**	**9a**	**10a**	**11a**	**12a**	**13a**	**14a**	**15a**
$^{3}J_{H,H}$ (Hz)	2.1[a]	2.3	1.9	1.8	2.6 2.5[c]	2.4[a] 1.6[a,c]	2.0	2.1	3.2 1.7[c]	1.8[a]	1.8[a]	2.2 2.2[c]	1.8[a]	2.2 2.1[c]	7.6[a] 2.9[a,c]
$^{2}J_{C^*,H}$ (Hz)	<1	<1	<1	<1	<1	<1 <1[c]	<1	<1	<1	<1	<1	<1	<1	<1	-4.2 -3.0[c]

compd	**1b**	**2b**	**3b**	**4b**	**5b**	**6b**	**7b**	**8b**	**9b**	**10b**	**11b**	**12b**	**13b**	**14b**	**15b**
$^{3}J_{H,H}$ (Hz)	2.8[a]	2.9	2.7	2.8[b]	5.6[c]	3.0[a,c]	2.8	2.6[c]	5.2[c]	2.8[a]	2.8	5.8[c]	2.6[a]	6.0[b]	8.8[a,c]
$^{2}J_{C^*,H}$ (Hz)	<1[d]	<1	<1	<1[b]	<1[d]	<1[d]	<1	<1[d]	<1[d]	<1	<1	<1[d]	<1	<1[b]	-5.8[d]

[a] measured from the ^{13}C satellite band, [b] solvent dioxane-d_8, [c] solvent $CDCl_3$, [d] solvent CD_2Cl_2

On the other hand large values $^{3}J_{H,H}$ (7.6 Hz) and $^{2}J_{H,C}$ (-4.2 Hz) for tetramethyltartramide **15a** are due to the predominant conformer G^- in polar alcohol solvent. Surprisingly, when measured in nonpolar chloroform solvent, $^{3}J_{H,H}$ and $^{2}J_{C^*,H}$ values for **15a** are correspondingly 2.9 Hz and -3.0 Hz. These data suggest that for **15a** there is considerable contribution of G^+ conformer in nonpolar solvents. Other dimethylamides (**5a**, **9a**, **12a**, **14a**) appear to have similar $^{3}J_{H,H}$ coupling constants in both alcohol and

chloroform solvents. Likewise, diester **6a** does not change the preferred *T* conformation on changing the polar alcohol solvent to less polar chloroform (Table 3). The previously low $^3J_{H,H}$ value for **6a** has been interpreted as an evidence for dominant G^+ conformer.[26]

Turning now to *O,O'*-dibenzoyl derivatives **1b-15b** we note that the $^3J_{H,H}$ values for *N,N*-dimethylamides **5b**, **9b**, **12b**, **14b** and **15b** are much higher (5.2-8.8 Hz) compared to the typical value 2.6-3.0 Hz observed for the remaining compounds **1b-4b**, **6b-8b**, **10b**, **11b** and **13b**. Such an increase of $^3J_{H,H}$ value is due to the large contribution of conformer G^-, in the case of **15b** calculated at 80% from the $^3J_{H,H}$ value 8.8 Hz.[66] In the case of *O,O'*-dibenzoyltartaronitriles **16-18** (Table 4) a large value of $^3J_{H,H}$ = 8.2 Hz was measured for a derivative **18** having the *N,N*-dimethylamide group, as opposed to derivatives **16** and **17** with $^3J_{H,H}$ =3.6-3.9 Hz. Again, in the case of **18** the conformer G^- contribution is estimated at 72%.[66]

Table 4. $^3J_{H,H}$ and $^2J_{C^*,H}$ values for tartaronitriles **16-18**

	16	**17**	**18**
$^3J_{H,H}$ (Hz) (solvent $CDCl_3$)	3.6	3.9	8.2
$^2J_{C^*,H}$ (Hz) (solvent CD_2Cl_2)	<1	<1/-2.5	-5.0/-6.0

Data of the Tables 3 and 4 show that a large (-5.0 to -6.0 Hz) $^2J_{H,C}$ value is observed only for *O,O'*-benzoylated dimethylamides **15b** and **18**, indicating a strong preference for conformer G^- in these cases. Other derivatives show low values of $^2J_{C^*,H}$ (typically less than 1 Hz) and this gives strong support for the predominance of conformer *T*. Finally we note that chemical shifts of C*-H protons (see Experimental) vary in a manner that qualitatively reflects the rotamer preference around the (O=)C-C(H) bond (Figures 1 and 3). Deshielding of the C*-H protons is expected in C=O/C*-OH synplanar rotamers (Fig. 1; Fig. 3, first row), while shielding is due to C=O/C*-OH antiplanar rotamers (Fig. 1; Fig. 3, third row). The lowest δ values are found for protons at C(α) to the $CONH_2$ and CONHMe groups, in accord with the preference for C=O/C-OH antiplanar conformation previously established by the CD measurements and the highest δ values are measured for protons at C(α) to the $CONMe_2$ group,[67] following the C=O/C*-OH synplanar or perpendicular preference established by the CD measurements. This may explain the difference between the δ values of protons α to the $CONMe_2$ and $CONH_2$ (or CONHMe) groups in diamides: **13a**, **14a** (ca. 0.4 ppm) and **13b**, **14b** (ca. 0.3 ppm).

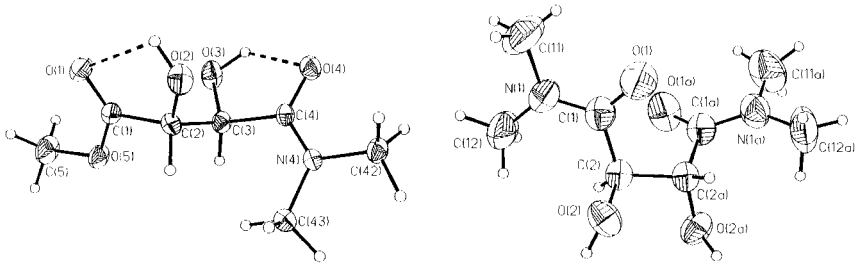
X-ray Crystallography.

Of all 30 (*R,R*)-tartaric acid derivatives (Chart 1), symmetrical and asymmetrical, bearing the methyl ester, amide, *N*-methylamide and *N,N*-dimethylamide groups (**1a** to **15a**) as well as their *O,O'*-dibenzoyl derivatives (**1b** to **15b**), ten X-ray crystal structure analyses have been completed so far. Full reports on X-ray results for compounds **1b**[68] (two independent crystal structure determinations) **6a**,[69] **7a**,[70] **15a** and **15b**[31] have already been published. In this paper we present the results of the crystal structure determinations for 4 compounds **9a**, **10a**, **12a** and **13a**. Selected torsion angles describing molecular conformation are listed in Table 5.

Table 5. Selected torsion angles and the angles between CO / C(β)H and CN / C(β)H bonds

Compound	C1-C2-C3-C4	O2-C2-C3-O3	O1=C1-C2-O2	O4=C4-C3-O3	CO / C(β)H	CN / C(β)H
6a (ref. 69)	-169.2(1)	-58.4(2)	-176.8(2)	0.2(2)	4.1	
					3.1	
7a (ref. 70)	171.8(3)	-73.1(3)	-3.6(3)	178.6(3)	-16.1	
	-175.1(3)	-63.0(3)	-176.9(3)	167.0(3)	-18.0	
					-17.9	
					-5.9	
9a	163.9(3)	-75.8(4)	12.5(5)	6.5(4)	-5.1	-13.7
	156.2(3)	-84.6(4)	12.8(5)	8.3(5)	-10.2	-19.6
10a	-167.0(2)	-54.2(3)	-178.2(2)	-179.4(2)	1.1	
					2.9	
12a	178.2(1)	-64.4(2)	-165.6(2)	21.6(2)	4.0	8.6
13a	173.2(5)	-69.1(6)	-178.4(6)	172.7(6)	-18.1	
					-11.2	
15a (ref. 31)	-52.4(2)	71.6(2)	90.5(3)		42.1	
1b (ref. 68)	173.5(6)	-68.5(6)	5.2(6)	-2.8(6)	-5.2	
					-0.5	
1b (ref. 68)	170.4(6)	-73.7(6)	4.6(5)	-1.1(6)	-5.6	
					-4.6	
15b (ref. 31)	-67.2(3)	60.3(2)	115.6(2)	57.7(3)	2.6	
					47.1	

Conformation around the C-C* bond.* As it follows from Table 5, for the vast majority of esters and amides, just as for the optically active tartaric acid,[11] the conformation found in the solid state by X-ray diffraction techniques is staggered, with a planar zigzag carbon chain and with carboxyl, amide or ester groups in *trans* orientation (*T* conformer in Figure 1). In this respect *N,N,N'N'*-tetramethyltartramide **15a**[31] and its *O,O'*-dibenzoyl derivative **15b**[31] constitute an exception since they both adopt the G^- conformation (Figure 1) in the crystal, in which the carbon chain is bent, the two bulky amide groups are *gauche* and the hydrogen atoms are *trans*. In the literature there are a few reports on the presence of the G^- conformation in the solid state. While the G^- conformation in the *O,O'*-dibenzoyl-(*R,R*)-hydrogen tartrate anion[71] is stabilized by the strong intramolecular hydrogen bonds, and in diisopropyl-(*R,R*)- tartrate it is forced by the unusual coordination around the titanium cations,[28] its presence in the structures of *N,N,N',N'*-tetraalkyltartramides, **15a** and **15b**, is not obvious. We are inclined to ascribe it to steric factors since the *T(s,s)* conformer (Figure 3, X=Y=NMe_2), consisting of two planar α-hydroxy-*N,N*-dimethylamide moieties in which the C(α)-OH (or OBz) bond nearly eclipses the C=O bond (as observed without exception in all *T* conformers studied so far) would cause unfavourable nonbonded H···H interactions between C* hydrogen atoms and methyl hydrogens of the NMe_2 group. This hypothesis is supported by the fact that in the crystal structure of the amidoester **9a** we observe a significant decrease of the C-C*-C*-C torsion angle to the values of 163.9(3) and 156.2(3)° in two crystallographically independent molecules. This bending of the carbon chain can be viewed as an attempt to minimize the repulsive forces between the hydrogen atoms while keeping the α-hydroxyamide group planar. In fact an attempt to optimize, by *ab initio* methods, the hypothetical *T(s,s)* conformer of **15a** (Figure 3) has failed, resulting in an eclipsed, rather than staggered rotamer. This staggered conformer is 4.96 kcal/mol higher in energy than the preferred $G^+(a,a)$ form (*vide Gas-Phase Calculations*). Figure 6 compares the *T* conformation of one of the molecules of **9a** with the G^- conformation of **15a** (note the lack of intramolecular hydrogen bonds in **15a**).



9a **15a**

Figure 5. Perspective view of the molecules **9a** and **15a** illustrating an extended (*T*) and bent (*G*$^-$) carbon chain conformation, respectively. Broken lines indicate intramolecular hydrogen bonds (note the lack of intramolecular hydrogen bonds in **15a**). The molecule of **15a** has a two-fold rotation axis coinciding with the crystallographic diad.

Conformation around the C-C bond.* As can be seen from Table 5, in (*R,R*)-tartaric acid esters and amides we observe a strong tendency to adopt a conformation in which an acid, ester or amide group, adjacent carbon atom and α-hydroxy or benzoyloxy oxygen are coplanar or nearly coplanar. CSD data[72] for the CCH(OR)-COOH type carboxylic acids (120 hits) as well as their esters (33 hits) and primary and secondary amides (28 hits) fully support this observation with only a few exceptions for acids. While in the α-hydroxyester residues of **1b**, **6a**, **7a** and **9a** there is no clear indication which of the two oxygen atoms eclipses the nearest hydroxyl (*i.e.* whether the conformation is of the *s* or *a* type, Figure 1b),[73] in primary and secondary amides it is always the amide nitrogen atom (the *a* conformer in Figure 1b). In tertiary amides the situation is more complex. Those with extended (*T*) carbon chain conformation (*i.e.* unsymmetrical mono-dimethylamides **9a** and **12a**) have carbonyl oxygen nearly eclipsing the α-hydroxyl oxygen The bent carbon chain form seems not to be favoured by the α-hydroxyamide planarity: of the three cases observed by us in **15a** and **15b**[31] one corresponds to the situation where the carbonyl oxygen is eclipsed by the β carbon atom, second where it is *synclinal* to this carbon and a third one, in the symmetric molecule **15a**, where C(β) is situated half way in between the two positions, the C*-C*-C=O torsion angle being -27.6(3)°. The three conformers can be described by one type designator *G*$^-$(*p*$^+$,*p*$^+$) using the convention described in Figure 1. The effect of conformational change around the C-C* bond upon substitution is illustrated in Figures 5 and 6.

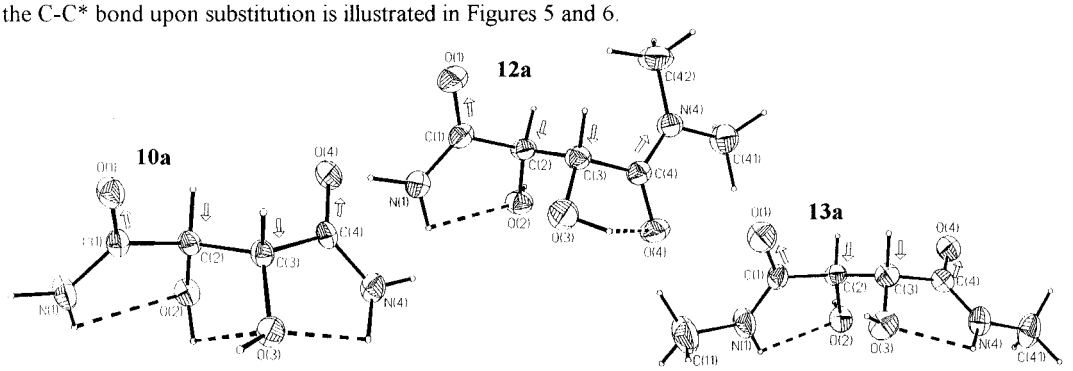
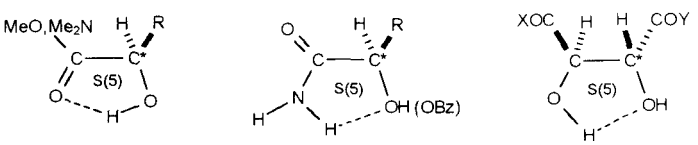


Figure 6. Illustration of a change in conformation around the C-C* bond in (*R,R*)-tartaric acid amides possessing an extended carbon chain skeleton. In tertiary amides (**12a**) hydroxyl oxygen is eclipsed by the carbonyl oxygen, while in primary (**10a**, **12a**) and secondary (**13a**) amides by the amide nitrogen atom. The conformations are stabilized by intramolecular hydrogen bonds (dashed lines) and attractive dipole-dipole interactions (dipoles marked with arrows).

In the literature, the few structures of the tertiary amides derived from CCH(OR)COOH type carboxylic acid[9,74] suggest that in these molecules there is a tendency for the C-O and C-C bonds to be ± *synclinal* to the carbonyl group. This is more in line with what we observe in the bent-carbon-chain conformers **15a** and **15b** (best representative, in this respect, being *N,N,N',N'*-tetracyclohexyl-*O,O'*-dimethyltartramide[9]) and contrasts with what is seen in *N,N*-dimethyltartramides with extended carbon chain (**9a** and **12a**). In these structures the tendency of the C*-OH bond to be eclipsed with the dimethylamide fragment prevails even though this leads to repulsion between the methyl hydrogens and the hydrogen atoms at chiral centers. To avoid these unfavourable interactions, the α-hydroxy-(or benzoyloxy)-dimethylamide fragment either becomes less planar, increasing the O-C*-C=O torsion angle to around 20°, as in structure **12a** (Figure 6) or the four-atom carbon chain bends slightly, decreasing the value of the C-C*-C*-C torsion angle to around 160°, keeping the O-C*-C=O fragment planar, as observed in the crystal structure of **9a** (Figure 5).

One consequence of the presence of the extended carbon chain conformation containing the two planar halves in mutual (-)*synclinal* orientation, (Fig. 3, first column) is the nearly parallel arrangement of the C-O (or C=O) and C(β)-H or C-N and C(β)-H bonds. The angles between the two bonds are in the range 0.5 to 19.6 ° with an average value of 8.8(6.2)° (Table 6). While in the majority of crystal structures geometrical parameters do not allow such a type of contact to be classified as intramolecular hydrogen bond of the C-H···O or C-H···N type, its apperance can be attributed to electrostatic interactions between negatively charged oxygen or nitrogen atoms and positively charged hydrogens at chiral centers.[75] The influence of these attractive forces on the molecular conformation might be significant owing to the fact that there are two such bond arrangements in one molecule.

Types of intramolecular hydrogen bonds. The presence of specific conformational isomers in the crystal is, to some extent, stabilized by the formation of intramolecular hydrogen bonds. Three major types of intramolecular hydrogen bonds which are observed in the crystal structures studied are presented schematically in Figure 7, and are listed below:



I II III

Figure 7. Types of intramolecular hydrogen bonds observed in the crystalline state: (I) αOH···O=C; (II) N-H···O(H)α; (III) O-H···O(H). All these H-bonds are described by one type of pattern designator S(5)[76].

1. Internal hydrogen bonding between the OH and the nearest ester or amide group (Figure 7,I) as found in two independent molecules of **9a** (Figure 5) and at the C(4) end of **12a** (Figure 6). In α-hydroxy ester moieties the acceptor might be one of two oxygen atoms, although the OH···O=C hydrogen bond prevails. This type of intramolecular hydrogen bond is formed only in tertiary amides (Figure 5, molecule **9a**; Figure 6, molecule **12a**) and is precluded in primary and secondary amides due to different conformational preferences of the latter.

2. Internal hydrogen bonding between the N-H and the OH groups from the same half of the molecule, as observed, without exception, in primary and secondary amide derivatives (Figure 7, II) and illustrated in Figure 6 for **10a** and **13a**. Formation of such a bond requires planar hydroxyamide grouping with C-N bond proximal and C=O bond distal to the hydroxyl oxygen atom. The observed conformational preferences of primary and secondary amides favour the formation of this type of hydrogen bond.

3. Internal hydrogen bonding between two vicinal hydroxyl groups (Figure 7, III). This might be reminiscent of the hydrogen bond present in isolated 1,2 diols. It is rarely observed, usually as a minor component in a more extensive system of intermolecular H-bonds (Figure 6, **10a**). In **10a** such an intramolecular hydrogen bond involves long H···O distance 2.44Å and O-H···O angle 103°. One manifestation of the presence of this type of hydrogen bond might be a slight decrease of the absolute value of the torsion angle O(2)-C(2)-C(3)-O(3) causing the two groups to come close together. This torsion angle reaches the value -54.2(2)° in **10a** as compared with the ideal value of -60° and with the average torsion angle -68.5(8.9)° of all ten conformers listed in Table 5.

Usually, though not always, these intramolecular interactions occur as minor components of three- and four-center hydrogen bonds, so they must be weak. However, the extent to which they are preserved in the solid state is quite high. The observed intramolecular interactions involve only proximal groups, thus no rings other than 5-membered are formed. In the graph-set notation[76] all these hydrogen-bond types might be described by one type of designator S(5). This contrasts with the situation in an isolated tartrate molecule, where, as a result of the presence of the internal hydrogen bonds between carbonyl oxygen and the β hydroxy hydrogen atoms, six membered rings, described by an S(6) pattern designator, are formed (*vide Gas-Phase Calculations*).

Besides imposing some rigidity to the molecule, intramolecular hydrogen bonds might play a key role in preserving the hydrogen bond cooperativity in the system.[77] Particularly in the case of tartaric acid derivatives, where the hydrogen bond functional groups are separated by a single covalent bond, intramolecular hydrogen bond joining proximal groups permits formation of infinite chains (**12a**), ribbons (**7a**), layers (**13a**) or three-dimensional networks (**10a**) composed exclusively of hydrogen bonds and stabilized by both σ- and π-cooperativity.[78]

Molecular mechanics.

Comparative MMX calculations were performed for rotamers of symmetrical derivatives **6a**, **10a**, **13a** and **15a**. Table 6 lists calculated lowest energy conformers of each type (*T*, G^-, G^+) with assignments according to Figures 1 and 3.

Table 6. MMX calculated lowest energy *T*, G^- and G^+ conformers of symmetrical derivatives of (*R*,*R*)-tartaric acid and their relative steric energy (kcal/mol).

MMX mode	**6a**		**10a**		**13a**		**15a**	
standard	*T(a,s)*	0.00	*T(a,a)*	0.00	*T(a,a)*	0.00	$G^-(s,s)$	0.00
calculation	$G^+(s,s)$	1.66	$G^+(a,s)$	1.34	$G^-(a,s)$	1.37	$G^-(a,s)$	0.72
	$G^-(s,s)$	2.08	$G^-(s,s)$	2.08	$G^+(s,s)$	3.92	*T(a,s)*	1.52
hydrogen	*T(a,s)*	0.00	$G^+(s,s)$	0.00	$G^+(s,s)$	0.00	$G^+(s,s)$	0.00
bonding	$G^+(a,s)$	1.36	*T(a,a)*	2.33	*T(a,a)*	2.77	*T(a,s)*	0.58
	$G^-(a,s)$	2.54	$G^-(a,s)$	3.35	$G^-(a,s)$	3.92	$G^-(s,s)$	0.96

Data of Table 6 reveal the preference for the *T* conformer of the diester **6a** and diamides **10a** and **13a** in the absence of intramolecular hydrogen bonding. In the intramolecular hydrogen bonding mode there is still a preference for the *T* conformer in the case of **6a,** but not in the case of diamides **10a** and **13a.** In these latter cases type II (Fig. 7) intramolecular hydrogen bonds stabilize the G^+ conformer, increasing the energy gap between G^+ and *T* conformers to more than 2.3 kcal/mol. Contrary, in the case of tetramethyldiamide **15a** the G^+ conformer is the preferred one regardless of the calculation mode but the steric energy difference between the three staggered conformers is quite small, compared to **10a** or **13a.** This is because, unlike in **10a** and **13a,** the structure of tertiary diamide **15a** cannot be stabilized by type II hydrogen bonding.

Quantum Chemical Calculations.

Semiempirical results. For each semiempirical method employed, three lowest energy conformers of **10a** and **15a** are presented in Tables 7 and 8, respectively.

Table 7. Selected semiempirical results for **10a**.

method	rotamer	relative energy [kcal/mol]	CC*C*C [°]	O=CC*O [°]	O=CC*O [°]	HOC*C* [°]	HOC*C* [°]
MNDO	*T(a,s)*	0.00	-157.4	-144.8	54.3	-97.3	64.5
	T(a,p$^+$)	0.04	-160.5	-147.8	90.1	-104.9	63.1
	G$^-$(s,s)	0.58	-63.7	56.3	56.2	57.2	57.1
AM1	*E$^-$(a,s)*	0.00	-101.2	158.4	12.9	32.7	84.9
	G$^+$(a,a)	0.20	57.8	159.2	159.1	52.8	52.9
	G$^-$(a,s)	1.52	-89.9	132.0	9.9	-7.6	98.1
PM3	*G$^+$(a,a)*	0.00	73.2	149.3	149.4	44.0	44.3
	G$^-$(a,s)	3.56	-91.6	170.9	3.8	-9.7	102.9
	G$^-$(p$^+$,p$^+$)	3.94	-68.3	61.4	61.5	57.4	57.8

Table 8. Selected semiempirical results for **15a**.

method	rotamer	relative energy [kcal/mol]	CC*C*C [°]	O=CC*O [°]	O=CC*O [°]	HOC*C* [°]	HOC*C* [°]
MNDO	*T(p$^+$, p$^+$)*	0.00	-152.0	82.6	77.7	-65.5	-66.1
	T(s,s)	0.20	-177.5	34.3	25.8	61.8	-164.3
	G$^-$(p$^+$,p$^+$)	0.21	-68.2	64.1	63.3	56.8	56.4
AM1	*E$^-$(a,s)*	0.00	-120.9	132.8	30.9	49.5	74.9
	G$^+$(a,a)	0.54	61.6	146.2	146.1	65.3	65.2
	E$^-$(p$^+$,p$^+$)	0.91	-105.1	109.8	109.1	53.9	53.5
PM3	*G$^-$(p$^+$,p$^+$)*	0.00	-80.1	60.2	60.1	56.1	56.3
	T(s,s)	1.05	-174.4	33.0	17.5	71.8	77.2
	T(p$^+$, p$^+$)	1.56	174.0	88.5	90.6	-40.4	-38.3

It is easy to notice, that the results of MNDO, AM1 and PM3 methods are contradictory. Whereas MNDO predicts for **10a** and **15a** several *T* conformers to be of low energy, the PM3 points to *G$^+$(a,a)* and *G$^-$(p$^+$,p$^+$)* for **10a** and **15a**, respectively (for definition of the conformers see Fig. 1). AM1 prefers an eclipsed arrangement of atoms around the C*-C* bond, however the *G$^+$(a,a)* conformer for both **10a** and **15a** is close, with an energy difference less than 0.6 kcal/mol. It is worth mentioning that the *G$^+$(a,a)* conformer, pointed out by the AM1 method for both **10a** and **15a**, and by the PM3 method for **10a** corresponds to the lowest energy structure obtained from *ab-initio* calculations (*vide infra*). Moreover, several conformers pointed out in the MNDO calculations were found to be unstable at RHF/3-21G level. It might be due to the well known behaviour of the MNDO method which provides a very poor description of hydrogen bonding and underestimates its energy.[79,80] In turn the AM1 procedure, developed in order to extinguish this MNDO shortcoming, generally overestimates the hydrogen bond energies and predicts bifurcated hydrogen bonds[70,49,80] which force the molecules to adopt eclipsed geometries. This can be a reasonable explanation of our AM1 results.

Ab-initio calculations. Results of *ab initio* calculations for **10a** and **15a** are presented in Tables 9 and 10 respectively.

Table 9. Results for **10a** molecule at HF/3-21G and HF/6-31G* level, after full optimization.

basis set	rotamer	relative energy [kcal/mol]	dipole moment [Debye]	CC*C*C [°]	O=CC*O [°]	O=CC*O [°]	HOC*C* [°]	HOC*C* [°]	H_2NC [1] [°]	H_2NC [1] [°]
3 - 21G	$G^+(a,a)$	0.00[2]	1.15	66.25	163.18	163.19	41.05	41.08	177.63	177.65
	$G^-(a,s)$	2.29	2.57	-94.91	170.57	-3.97	-23.72	123.65	177.00	-178.47
	$G^+(s,s)$	3.54	0.32	51.59	-12.63	-12.60	143.57	143.56	-175.82	-175.80
	$T(a,a)$	6.28	0.84	151.11	159.64	159.66	-56.72	-56.71	172.70	172.72
	$T(a,a)$	9.45	3.75	-178.29	142.98	172.28	39.17	-82.22	174.22	179.01
	$G^+(a,s)$	13.98	8.07	49.64	160.00	-10.13	-82.01	78.53	173.48	-173.28
	$E^-(a,a)$	16.24	4.08	-134.23	153.35	153.42	61.14	61.06	-177.33	-177.36
	$T(s,s)$	16.56	5.97	149.75	1.28	1.18	114.15	114.24	-166.93	-166.96
	$T(a,s)$	17.23	3.68	176.75	-160.16	4.86	-170.52	106.80	161.68	177.20
	$T(a,s)$	23.12	6.10	151.97	165.18	2.68	-63.44	-65.34	172.02	154.80
	$G^-(s,s)$	25.58	6.61	-103.77	26.32	26.32	78.21	78.21	-167.79	-167.79
	$G^-(a,a)$	27.25	5.20	-55.81	-156.42	-156.42	2.28	2.28	167.56	167.56
6 - 31G*	$G^+(a,a)$	0.00[3]	0.82	62.58	160.32	160.39	48.45	48.49	170.84	170.82
	$G^+(s,s)$	3.16	0.06	51.68	-10.39	-10.44	145.73	145.74	-172.40	-172.44
	$G^-(a,s)$	3.27	2.68	-94.15	172.55	1.35	-25.69	121.71	174.68	-172.74
	$T(a,a)$	3.64	1.40	168.35	154.58	154.52	-68.79	-68.84	162.20	162.18
	$T(a,a)$	5.79	3.76	-175.14	141.63	176.51	45.09	-79.39	168.01	-174.25
	$T(a,s)$	7.21	2.06	-160.36	175.82	2.36	34.77	129.56	-173.55	164.98
	$G^+(a,a)$	8.18	1.47	53.33	143.10	175.13	49.96	-138.66	156.72	143.37
	$T(s,s)$	10.29	2.58	161.59	-23.80	-23.87	144.96	144.94	-139.13	-139.36
	$T(a,s)$	10.48	2.98	-175.48	-166.42	10.98	-165.09	103.37	147.39	158.62
	$G^+(a,s)$	11.45	7.23	49.02	155.19	-3.88	-77.94	100.49	163.16	-162.72
	$T(a,a)$	11.97	3.78	-148.52	160.99	161.00	69.48	69.85	-155.40	-155.23
	$G^-(a,a)$	15.62	3.13	-26.96	-157.46	-157.81	-157.11	-156.48	154.42	155.17

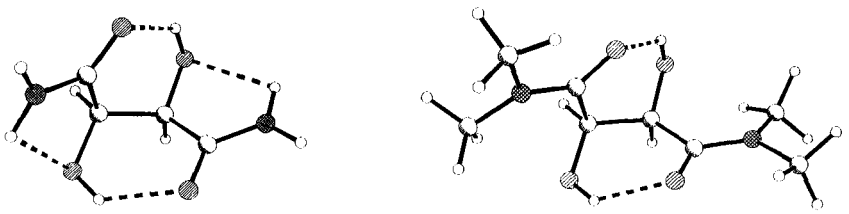
[1] H_2NC angle is an dihedral between planes: ^{E}H-N-C(=O) and (O=)C-N-^{Z}H and describes pyramidalization of N atom
[2] Energy at 3-21G basis set was: -561.3848672252 Hartree.
[3] Energy at 6-31G* basis set was: -564.5148483793 Hartree.

Table 10. Results for **15a** molecule at HF/3-21G and HF/6-31G* level, after full optimization.

basis set	rotamer	relative energy [kcal/mol]	dipole moment [Debye]	CC*C*C [°]	O=CC*O [°]	O=CC*O [°]	HOC*C* [°]	HOC*C* [°]	H_2NC [1] [°]	H_2NC [1] [°]
3 - 21G	$G^+(a,a)$	0.00[2]	0.54	63.52	141.71	141.89	58.70	58.86	-175.84	-175.68
	$G^+(s,s)$	6.23	0.83	49.29	22.87	22.86	103.27	103.30	172.12	172.13
	$E^-(a,s)$	6.62	3.10	-139.19	159.51	4.57	24.48	120.68	-175.63	172.23
	$E^+(s,s)$	8.75	5.09	121.16	11.12	11.06	108.34	108.45	-162.82	-162.79
	$G^-(a,s)$	12.73	4.44	-77.67	-147.62	24.25	-36.46	99.98	-178.40	-173.64
	$G^-(s,s)$	14.77	5.81	-53.26	41.68	41.51	85.37	85.52	174.16	174.15
	$G^+(a,s)$	14.88	5.57	67.43	128.70	10.53	54.78	73.67	-173.68	140.96
	$G^-(a,a)$	18.89	4.13	-52.55	-139.64	-143.88	-170.96	-48.67	167.70	174.67
	$T(a,a)$	19.09	4.96	-170.11	-161.70	-162.19	-166.12	-165.35	166.67	166.59
6 - 31G*	$G^+(a,a)$	0.00[3]	0.19	65.54	139.95	140.14	59.64	59.81	-173.59	-173.26
	$G^+(s,s)$	2.72	0.99	49.93	25.53	25.54	103.60	103.60	166.15	166.15
	$E^+(s,s)$	4.96	5.11	129.37	16.08	16.08	104.04	104.04	-157.73	-157.73
	$T(a,s)$	5.28	3.15	-152.00	160.20	8.95	39.19	118.33	-161.91	164.73
	$G^-(s,s)$	6.90	4.91	-57.72	47.06	46.90	81.17	81.30	169.07	169.06
	$G^-(a,s)$	7.25	4.41	-69.43	-149.03	31.68	-43.52	95.25	179.15	-166.44
	$G^+(s,p^+)$	9.20	4.09	62.31	4.86	90.56	113.46	68.25	143.24	169.89
	$T(a,a)$	11.91	4.90	-170.58	-159.91	-159.86	-166.42	-166.48	153.25	153.35
	$G^-(a,a)$	19.88	4.00	-49.06	-133.35	-142.64	-171.91	-47.71	159.89	161.64

[1] H_2NC angle is an dihedral between planes: ^{E}H-N-C(=O) and (O=)C-N-^{Z}H and describes pyramidalization of N atom.
[2] Energy at 3-21G basis set was: -716.6233960038 Hartree.
[3] Energy at 6-31G* basis set was: -720.6107234539 Hartree.

For both molecules **10a** and **15a** the lowest energy conformer predicted by the *ab-initio* method up to RHF/6-31G* level is the $G^+(a,a)$ one (Figure 8).



10a **15a**

Figure 8. Lowest energy structures of **10a** and **15a** after full optimization at RHF/6-31G* level.

This conformer is stabilized by two hydrogen bonds, each closing a six membered ring by joining carbonyl oxygen with β-hydroxyl hydrogen. The D···A and A···H distances are 2.749Å, 1.971Å and 2.593Å, 1.822Å for **10a** and **15a** diamides respectively. It is worth noting that the lowest energy structure converged to a conformer possessing C_2 symmetry and in the case of **10a** the $G^+(a,a)$ conformer is additionally stabilized by two hydrogen bonds between the amide hydrogen and the α hydroxyl oxygen, each closing a five membered ring (Figure 8). A similar G^+ structure of dimethyl tartrate in nonpolar solvent was postulated by Su and Keiderling[26b] on the basis of their NMR and VCD studies.

The arrangement of hydrogen bonds leading to the formation of two six membered rings is also observed in the most stable of all T rotamers of **10a**. At RHF/6-31G* level, this conformer is by 3.6 kcal/mol higher in energy, compared to $G^+(a,a)$. However, in this $T(a,a)$ conformer there are no hydrogen bonds of the N-H···O(H) type, which bring additional stabilization to the $G^+(a,a)$ form.

Energy differences between $G^+(a,a)$ conformers and all remaining rotamers amount to at least 3.2 kcal/mol and 2.7 kcal/mol for **10a** and **15a** respectively. The $T(a,a)$ rotamer of **10a,** closely resembling that found in the solid state, is by 5.8 kcal/mol higher in energy. In the case of tetramethyl tartamide **15a** it is difficult to define unequivocally the conformer that matches the one present in the crystal structure. The closest conformer $G^-(s,s)$ has an energy higher than $G^+(a,a)$ by 6.9 kcal/mol.

Surprisingly, for **15a** $T(s,s)$ structure converged during full optimization to an eclipsed conformer $E^+(s,s)$ and in $T(a,s)$ the C-C*-C*-C angle converged to the value of 152°, which is almost exactly between the ideal trans and eclipsed forms (Figure 9). This seems to be caused by repulsion between the methyl substituent from the amide group and the hydrogen atom attached to the β carbon atom. The distance between these groups is increasing simultaneously to the bending of the main carbon chain.

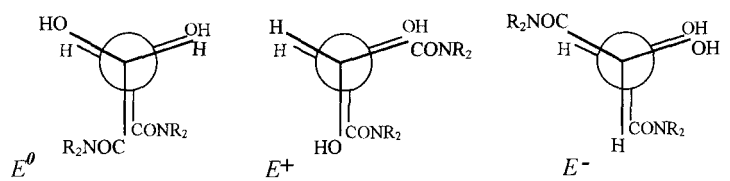


Figure 9. Eclipsed conformers are named E^0, E^+ and E^- with respect to different value of C-C*-C*-C torsion angle (about 0°, +120° and -120°, respectively).

The possibility of formation of hydrogen bonds is the main factor that influences adoption of a particular conformation by each of the molecules studied and seems to play a vital, stabilizing role. With only one exception for

the *T(a,a)* conformer of diamide **15a,** all obtained conformers have intramolecular hydrogen bonds. However, it should be stated that hydrogen bonding is by no means the only factor. Conformer *T(a,a)* and several other *T* and G^- conformers of **10a** and **15a** are additionally stabilized by attractive interactions between antiparallel dipoles O=C and C(β)-H.

The formation of hydrogen bonds is evident not only from geometrical parameters, but from the electronic structure as well. Generally, hydrogen atoms that are involved in hydrogen bond formation gain some positive charge, while oxygen atoms acting as hydrogen bond acceptors, increase their negative charge. For example in the case of the most stable conformation, the charge (due to Mulliken analysis at the HF/6-31G* level) on both hydroxyl hydrogens that are involved in hydrogen bonding amounts to +0.496e and +0.494e in **10a** and **15a** respectively. The corresponding charges on carbonyl oxygens acting as acceptors are -0.659e and -0.681e. In the $G^+(a,s)$ conformer of both **10a** and **15a** we observe a situation in which only one hydroxyl hydrogen is engaged in the hydrogen bond by forming a three-center bond. In **10a** the charge on this hydrogen is +0.486e, while on the other not involved in hydrogen bond is only +0.462e. Similarly, in the $G^+(a,s)$ conformer of **15a** the positive charge on the hydroxyl hydrogen involved in the hydrogen bond is +0.489e, whereas on the other only +0.469e.

Similarly, when a hydrogen bond is formed in which the amide nitrogen acts as a donor and α-hydroxyl oxygen as an acceptor, as in the case of **10a**, different charges on amide hydrogens are observed. The charge on *E*-hydrogen involved in the hydrogen bond is +0.422e, whereas that on the *Z*-hydrogen is +0.401e.

It is well known[81] that a larger negative charge on the oxygen atom due to a hydrogen bond would lead to stronger resonance within the amide group. Consequently this should increase the resistance to out of plane bending at nitrogen. Indeed, after optimization at the RHF/3-21G and RHF/6-31G* levels nitrogen atoms are in sp^2 hybridization i.e. are planar, when the amide group is involved as a donor in the hydrogen bond. At 3-21G basis set the three atoms surrounding a nitrogen atom form a plane even more often. The only possibility of partial pyramidalization of nitrogen at that relatively small basis set is the formation of a hydrogen bond in which this nitrogen acts as an acceptor. For the *T(a,s)* conformer of **10a** we found the C(sp^2-)-N bond lengths equal to 1.329Å and 1380Å for planar and partially pyramidalized nitrogen atoms. And for the $G^+(a,s)$ conformer of **15a** the corresponding bond lengths are 1.345Å, 1.392Å. Pyramidalization of the nitrogen atom should lead to a decrease of the negative charge of the amide oxygen. The calculated charges on amide oxygens support the above statement. Indeed the charges on the oxygen close to planar nitrogen are -0.676e, -0.660e for **10a** and **15a** whereas the corresponding values for oxygen next to partially pyramidalized nitrogen are -0.573e, -0.587e, respectively.

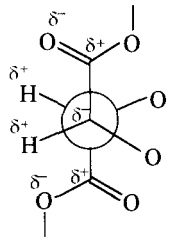
Contrary to the RHF/3-21G results calculations at the RHF/6-31G* level gave different indications concerning the planarity of the amide nitrogen. The NH_2, or NMe_2 groups were planar only when the amide group was involved in the hydrogen bond. In all other cases the nitrogen atom was partially pyramidalized. It is in agreement with the results of Sulzbach et al.,[82] who examined the correlation between the NMR chemical shift and the pyramidalization of the amide nitrogen in dipeptide analogues.

DISCUSSION

The parent molecule for tartaric acid is succinic acid (butanedioic acid) and the intermediate structure belongs to malic acid (2-hydroxybutanedioic acid). While X-ray determined structures indicate a planar *T* conformation of the four carbon chain in each of the three acids, conformational similarities cannot be extended to their derivatives. Both *G* and *T* conformers are found in the crystal structures of esters, amides and salts of succinic acid;[83] in one case two crystallographically independent molecules of different conformation co-exist in

a crystal of a monoamide of succinic acid despite the fact that they form the same hydrogen bonding pattern.[84] In addition, a "natural" *T* conformation of the carbon chain of succinic acid, in which the two polar carboxy groups are kept apart, is not entirely supported in solution, as shown by NMR studies.[85-86]

Our present study embodies (*R,R*)-tartaric acid derivatives with all combinations of methyl ester, amide, *N*-methylamide and *N,N*-dimethylamide functional groups. The corresponding *O,O'*-dibenzoyl derivatives as well as some nitriles are also included. The methods applied allowed us to make conformational assignments for these derivatives in widely differing environments. Although the data obtained point to different dominant conformers for different types of tartaric acid derivatives under varying conditions, we are nevertheless in position to pinpoint only a few structural factors to account for the observed conformational diversities. It is apparent from this study that a significant role in determining the conformation of tartaric acid derivatives can be ascribed to hydrogen bonding (either intra - or intermolecular), including OH and NH donor groups. Further effects are of an electrostatic nature and involve electrostatic interactions between coplanar or nearly coplanar CO and C(β)H and/or CN, C(β)H bonds (**25**). In addition, in the case of *N,N*-dimethyltartramides there is a significant steric effect involving the methyl group anti to the amide carbonyl group.



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Tartaric acids and tartrate ions have been viewed as consisting of two planar halves containing hydroxyacetic acid groups. As it follows from our investigations, this approach can be extended to esters and primary or secondary amides of (*R,R*)-tartaric acid in the solid state and in polar solvents. Planarity of these groups has been discussed in the literature[87] with the conclusion that the presence of intramolecular H bond is not a necessary condition for it to occur. This is also in line with our observations: in the *T* conformer the C(α)-O bond is always in the plane or nearly in the plane of the acid, amide or ester group in spite of the absence of an intramolecular hydrogen bond, which may be due to a dominance of intermolecular hydrogen bond interactions or due to a lack of proton donors resulting from *O*-benzoylation. In the majority of cases, however, the internal hydrogen bond is retained in the crystal, bringing additional stability to the fragment and leading to the formation of hydrogen bonded five membered rings, S(5), Figure 7. *Ab initio* calculations on the parent acid **1a**[19] also point out to the existence of hydrogen bonds with the S(5) motif. On the other hand, our *ab initio* calculations on diamides **10a** and **15a** indicate that the preference to keep the α-OH substituent in the plane of the amide fragment is limited to only these cases where such a system is stabilized by intramolecular hydrogen bond.

In (*R,R*)-tartaric acid derivatives the existence of the two planar halves is invariably connected with the staggered *T* conformation around the central C*-C* bond and a planar zig-zag carbon chain. As a result, two hydrogen-bonded S(5) rings have a relative orientation controlled by the chirality of the asymmetric carbon atoms. Such an arrangement of the substituents is additionaly stabilized by electrostatic interactions between the coplanar CO/C(β)H and CN/C(β)H bonds[75] (**25**). The dominance of this spatial orientation of substituents in the solid state and in polar solvents is overwhelming.

Turning now to the intriguing case of the *N,N*-dimethylamide group we note that in molecules with such a substituent the *T* conformer is destabilized by steric interactions between the C(β)-H and the amide

methyl group. In the asymmetrically substituted *N,N*-dimethyltartramides, which contain only one such group, significant bending of the carbon chain (observed for example in the crystal structure of **9a**, Table 5) might be viewed as a result of a compromise between steric hindrance and a tendency towards planarity. In these compounds the percentage of the *T* conformer in solution drops significantly as shown by CD measurements (Table 2) and by NMR data (Table 3). The strain would be doubled in the symmetrically substituted *N,N*-dimethyltartramides in the *T(s,s)* conformation. This could be avoided by adopting different conformation at both ends of the molecule, *i.e. T(a,s)*. However, an attempt to optimize the *T(a,s)* rotamer by *ab initio* methods leads to a significant bending of the carbon main chain. This not only minimizes unfavourable steric interactions but also maximizes the number of internal hydrogen bonds by allowing the formation of hydrogen bonds of type I and III (Figure 7). As might be expected, such a form is not of the lowest energy and it differs from the preferred *G'(a,a)* conformation by nearly 5 kcal/mol (6-31G* level). Consequently, in the solid state and in polar solvents the *N,N,N',N'*-tetraalkyltartamides no longer exist in an extended carbon chain *T* form, but adopt a bent carbon chain conformation *G⁻*. Planarity of the α-hydroxy-*N,N*-dialkylamide fragment is not retained,[88] but in such conformation CO/C(β)H electrostatic interactions might still operate, in the absence of intramolecular hydrogen bonds. For example, the conformation of amides **15a** and **15b** is shown as *G⁻* in solution and *G⁻(p⁺,p⁺)* in the crystal.

One interesting result of our calculations on diamides **10a** and **15a** is the pronounced tendency of isolated molecules to form fully intramolecularly hydrogen-bonded minimum energy *G'(a,a)* conformers, in which all potential hydrogen bond donor and acceptor groups are optimally oriented. These results show that the influence of intramolecular hydrogen bonding on the preference for a certain conformation is dominant. Moreover, the *G'(a,a)* conformer has the lowest value of the molecular dipole moment, so in the absence of other factors, it should be energetically preferred for an isolated molecule. In **10a,** the *G'(a,a)* conformer is stabilized by two types of hydrogen bonds: C=O···HO-C(β), described by S(6) designator, and N-H···O(H), forming S(5) motif. From what we have learned so far, we might expect, that for diamide **13a** the lowest energy conformer would also be *G'(a,a)* with the same pattern of hydrogen bonds. Incidentally, MMX calculations gave similar results for **10a** and **13a**, although different from *ab initio*, their lowest energy *G'(s,s)* structures being stabilized by a OH···O=C hydrogen bond, designated by S(5) motif, as well as by N-H···O-C(β) hydrogen bond of the S(6) motif. Recent *ab initio* quantum mechanical studies showed the intrinsic tendency of the *N,N'*-dimethylsuccinamide molecule to adopt a folded *G* conformation, irrespective of the environment,[89] due to formation of an intramolecular hydrogen bond of S(7) motif between the amide hydrogen and the oxygen atoms from two different halves of the molecule. On the other hand, in the solid state the two diamides **10a** and **13a** form extensive intermolecular hydrogen bonds between the molecules in the preferred *T(a,a)* conformation and this results, *inter alia*, in their high melting points (**10a**: 205-207°; **13a** 198-200°) and virtual insolubility in nonpolar solvents. NMR and CD data for solutions in polar solvents also indicate the *T(a,a)* conformer as the most stable one and identical preference is shown by MMX calculation in the absence of an internal hydrogen bond.

In an isolated molecule of tertiary diamide **15a** the *G⁺(a,a)* conformer, predicted as the lowest energy by *ab initio* calculations, is stabilized by the C=O···HO-C(β) hydrogen bonds, described by S(6) designator. The *G'(s,s)* conformer is less favourable by 2.72 kcal/mol, but other conformers *i.e. T(a,s)* and *E'(s,s)* (appearing as a result of optimization of the *T(s,s)* conformer) follow quite closely, the difference not exceeding 5.3 kcal/mol. Synplanar conformers are stabilized by a hydrogen bond of the S(5) motif. Significantly, the presence of the *G⁺* conformer of **15a** in nonpolar solvent follows from NMR measurement in $CDCl_3$ solution, while the *G⁻* conformer is found in polar solvents and in the crystal. This nicely demonstrates that conformation of tartaric acid diamides is highly influenced by the interactions with the environment.

CONCLUSIONS

The results described here indicate that the *T* conformer of (*R,R*)-tartaric acid, its esters and amides is preferred in polar media and in the solid state. The G^+conformer is definitely energetically favoured for isolated (*R,R*)-tartaric acid derivatives which form hydrogen bonds with OH donors, while the G^- form might dominate among those derivatives which lack such possibility. The latter rotamer, as well as the *T* conformer, might be stabilized by electrostatic interactions between the coplanar CO/C(β)H and CN/C(β)H bonds.

The origin of the strong conformational bias among (*R,R*)-tartaric acid derivatives stems from the fact that these molecules, containing several hydrogen-bonding and polar groups, tend to adopt in the solid state and in polar solvent such form which will maximize intermolecular interactions. Analysis of intra- and intermolecular non-bonded interactions in (*R,R*)-tartaric acid esters and amides leads to the conclusion that these are mostly electrostatic in nature, even in the structures with an extended hydrogen bonding system. This is manifested by the tendency to form many, consequently rather weak, hydrogen bonds in which carbonyl groups act as multiple acceptors while amide and hydroxyl hydrogen atoms act as multiple donors. Weak hydrogen bonds are primarily electrostatic, less directional and the long range interactions.

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EXPERIMENTAL

General. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer at 300 and 75 MHz, respectively, using TMS as internal standard. IR spectra were obtained with a Bruker IFS 113 v FT-IR spectrometer. Elemental analyses were performed on a 2400 CHN Perkin-Elmer Elemental Analyzer by Chem Anal Lab in Poznan. High resolution mass spectra were obtained with an AMD-604 instrument. Specific rotations were determined with a Perkin-Elmer 243 MB polarimeter. Circular dichroism spectra were recorded with a Jobin-Yvon Dichrograph III. UV spectra were recorded with a Shimadzu UV 160 spectrophotometer. Melting points were determined on a Koffler block and are uncorrected. Column chromatography was carried out with Macherey - Nagel silica gel 60 (100 - 200 mesh). TLC analyses were performed with Merck TLC plastic sheets silica gel $60F_{254}$. Solvents and reagents were purified, when necessary, according to standard procedures.

Compounds **1a**, **1b**, **5b**, **6a**, and **15a** are commercial. Compounds **2a**,[90] **2b**,[91] **3a**,[92] **7a**,[93] **10a**,[94] **13a**,[94,95] (+)-*O,O'*-dibenzyl tartrate (**21**)[96], (+)-*O,O'*-diacetyltartaric anhydride (**19**)[91,97] and (+)-*N*-methyltartrimide (**22**)[98] were prepared according to the literature. (+)-*O,O'*-Dibenzoyltartaric anhydride (**20**) was prepared according to literature[99,100] except that the isolation of the product was facilitated by the addition of dioxane (100 mL) and benzene (100 mL) to the hot reaction mixture and allowing the anhydride to crystallize. Yield 85-90%, m. p. 166-168°.

(*R,R*)-(+)-Tartaric acid (1a). ^{1}H NMR (CD_3OD) δ 4.55 (s, CH); ^{13}C NMR (CD_3OD) δ 73.3 (d, J = 146.0 CH), 174.5 (C=O).

Monomethyl (*R,R*)-(+)-tartrate (2a).[90] ^{1}H NMR (CD_3OD) δ 3.77 (s, 3H, OMe), 4.51 (d, J = 2.3 Hz, 1H, CH), 4.57 (d, J = 2.3 Hz, 1H, CH); ^{13}C NMR (CD_3OD) δ 52.8 (q, J = 147.5, OMe), 73.4 (d, J = 145.4 Hz, CH), 73.7 (d, J = 146.5 Hz, CH), 173.3 and 174.2 (C=O).

(*R,R*)-(+)-Tartaric acid monoamide (3a).[92] ^{1}H NMR (CD_3OD) δ 4.42 (d, J = 1.9 Hz, 1H, CH), 4.54 (d, J = 1.9 Hz, 1H, CH); ^{13}C NMR (CD_3OD-D_2O) δ 72.5 (d, J = 146.1, CH), 73.4 (d, J = 146.1 Hz, C-H), 175.6 and 177.1 (C=O).

(*R,R*)-(+)-Tartaric acid mono(*N*-methylamide) (4a). To a solution of anhydride **19** (2.16 g, 10 mmol) in THF (10 mL) was added 5.5 M $MeNH_2$ in THF (10 mL) and the reaction mixture was stirred overnight at room temperature. The methylammonium salt of **4a** was filtered off, washed with diethyl ether and stirred with 7 g Dowex 50 W resin in THF (10 mL). The Dowex resin was filtered off and the filtrate evaporated. The residue was dissolved in AcOEt and the solution dried over $MgSO_4$. After removal of solvents product **4a** was crystallized from AcOEt - hexane, yield 0.95 g (58%), m. p. 154-156°; ^{1}H NMR (CD_3OD) δ 2.80 (s, 3H, NMe), 4.45 (d, J = 1.8 Hz, 1H, CH), 4.56 (d, J = 1.8 Hz, 1H, CH); ^{13}C NMR (CD_3OD) δ 26.1 (q, J = 138.2 Hz, NCH_3), 73.0 (d, J = 145.3 Hz, CH), 74.2 (d, J = 144.9 Hz, CH), 174.5 and 175.1 (C=O); IR (KBr) 3600-2400 (COOH), 3470, 3370 and 3320 (OH and NH), 1730 and 1620 (C=O) cm^{-1}; $[\alpha]^{20}_D$ +86.8° (c 1.0, H_2O); Anal. Calcd. for $C_5H_9NO_5$: C, 36.81; H, 5.56; N, 8.59. Found: C, 36.79; H, 5.47; N, 8.53.

(*R,R*)-(+)-Tartaric acid mono(*N,N*-dimethylamide) (5a). A solution of 3.3 g (10 mmol) (+)-dibenzyl tartrate (**21**)[96] in anhydrous THF (10 mL) was stirred at room temp. for 5 days with 2.35 M dimethylamine in THF (10 mL). The solvents were removed in vacuo at 60°C and the mixture (2.6 g) was separated by column chromatography on silicagel (CH_2Cl_2 - CH_3OH, 20:1 and 10:1) to give unreacted dibenzyl tartrate (0.7 g), diamide **15a** (0.2 g, 10%), m. p. 186-188°, and tartaric acid mono (*N,N*-dimethylamide) monobenzyl ester, m. p. 76-81°, (0.9 g, 34%); ^{1}H NMR ($CDCl_3$) δ 3.04; 3.07 (two singlets, 6H, NMe_2), 3.20 (br s, 1H, OH), 4.24 (d, J= 5.1 Hz, 1H, CH), 4.42 (br s, 1H, OH), 4.77 (d, J = 5.1 Hz, 1H, CH), 5.30 (dd, 2H, CH_2), 7.38 (m, 5H, C_6H_5); IR (film) 3400 (OH), 1743 and 1642 (C=O) cm^{-1}. Tartaric acid mono(*N,N*-dimethylamide) monobenzyl ester (250 mg) in CH_3OH (2 mL) was hydrogenated at ambient temperature and pressure over palladium hydroxide on carbon, 20% Pd (20 mg). After 2 h the catalyst was filtered off and the solution evaporated to dryness to give **5a** (160 mg, 96%) as thick oil: ^{1}H NMR (CD_3OD) δ 2.98 and 3.14 (two s, 6H, NMe_2), 4.37 (d, J = 2.6 Hz, 1H, CH), 4.85 (d, J = 2.6 Hz, 1H, CH); ^{13}C NMR (CD_3OD) δ 36.4 (q, J = 138.5 Hz, NMe), 37.2 (q, J = 138.2 Hz, NMe), 71.3 (d, J = 147.6 Hz, CH), 72.4 (d, J = 144.2 Hz, CH), 172.4 and 174.9 (C=O); IR (film) 3600-2500 (COOH), 1742 and 1643 (C=O) cm^{-1}; $[\alpha]^{20}_D$ +3.6° (c 1.0, CH_3OH). Exact mass for $C_6H_{12}NO_5$ (M^+ + H): calcd 178.0715; Found 178.0712.

Dimethyl (*R,R*)-(+)-tartrate (6a). ^{1}H NMR (CD_3OD) δ 3.77 (s, 6H, OMe), 4.55 (s, 2H, CH); ^{13}C NMR (CD_3OD) δ 52.9 (q, J = 148.1 Hz, OMe), 73.4 (d, J = 147.1 Hz, C-H), 173.0 (C=O).

(*R,R*)-(+)-Tartaric acid monoamide monomethylester (7a).[93] ^{1}H NMR (CD_3OD) δ 3.78 (s, 3H, OMe), 4.40 (d, J = 2.0 Hz, 1H, CH), 4.58 (d, J = 2.0 Hz, 1H, CH); ^{13}C NMR (CD_3OD) δ 52.7 (q, J = 147.3 Hz, OMe), 73.4 (d, J = 145.8 Hz, CH), 74.2 (d, J = 146.1 Hz, CH), 173.9 and 176.7 (C=O).

(*R,R*)-(+)-Tartaric acid mono(*N*-methylamide) monomethyl ester (8a). A solution of **4a** (163 mg, 1mmol) in methanol (5 mL) was methylated with ethereal diazomethane; the solvents were removed in vacuo and the residue crystallized from methanol - diethyl ether, yield of **8a** - 145 mg (82%), m. p. 139-143°; ^{1}H NMR (CD_3OD) δ 2.79 (s, 3H, NMe), 3.78 (s, 3H, OMe), 4.41 (d, J = 2.1 Hz, 1H, CH), 4.58 (d, J = 2.1 Hz, 1H, CH); ^{13}C NMR (CD_3OD) δ 26.1 (q, J = 138.1 Hz, NMe), 52.7 (q, J = 147.2 Hz, OMe), 73.4 (d, J = 146.5 Hz, CH), 74.2 (d, J = 145.5 Hz, CH), 173.9 and 174.2 (C=O); IR (KBr) 3440, 3360, 3235 (OH and NH), 1752, 1737, 1660, 1650 (C=O); $[\alpha]^{20}_D$ +130.5° (c 1.0, H_2O). Anal. Calcd. for $C_6H_{11}NO_5$: C, 40.68; H, 6.26; N, 7,91. Found: C, 40.28; H, 6.22; N, 7.82.

(*R,R*)-(+)-Tartaric acid mono(*N,N*-dimethylamide) monomethyl ester (9a).

A. 4.32 g (20 mmol) anhydride **19** was dissolved in THF (10 mL) and stirred for 1h at room temp. with 7.8 M Me_2NH in dimethoxyethane (4 mL). The solvents were removed *in vacuo* and the residue dissolved in CH_2Cl_2 and extracted with a mixture of 6N HCl (4 mL) and brine. After removal of solvents and crystallization from AcOEt 3.8 g (73%) of *O,O'*-diacetyltartaric acid mono (*N,N*-dimethylamide) was obtained, m. p. 158-162°; ^{1}H NMR (CD_3COCD_3) δ 2.08 (s, 6H, OAc), 2.88 and 3.16 (two s, 6H, NMe_2), 5.66 (d, J = 4.4 Hz, 1H, CH), 5.86 (d, J = 4.4 Hz, 1H, CH). The amide (1 g) was dissolved in methanol (10 mL) and methylated with excess etheral diazomethane. The solvents were removed *in vacuo* and the residue redissolved in methanol and stirred overnight with KCN (50 mg). Methanol was evaporated *in vacuo* and the product purified by chromatography on silicagel (solvent CH_2Cl_2 - 1.5% methanol). Product **9a** (0.64 g, 88%) slowly crystallized on standing and was recrystallized from AcOEt - diethyl ether, m. p. 48-51°; ^{1}H NMR (CD_3OD) δ 2.98 and 3.13 (two s, 6H, NMe_2), 3.78 (s, 3H, OMe), 4.45 (d, J = 3.2 Hz, 1H, CH), 4.80 (d, J = 3.2 Hz, 1H, CH); ^{13}C NMR (CD_3OD) δ 36.3 (q, J = 138.4 Hz, NMe), 37.2 (q, J = 138.6 Hz, NMe), 52.7 (q, J = 147.5 Hz, OMe), 71.6 (d, J = 147.7 Hz, CH), 72.9 (d, J = 145.4 Hz, CH), 172.1 and 173.3 (C=O); IR (KBr) 3370 (OH), 1748, 1642 (C=O) cm^{-1}; $[\alpha]^{21}_D$ - 20.0° (c 1.0, MeOH). Anal. Calcd. for $C_7H_{13}NO_5$: C, 43.98; H, 6.95; N, 7.33. Found: C, 44.11; H. 6.96; N, 7.27.

B. **9a** could also be prepared from **6a** by prolonged action of one molar equivalent of Me_2NH in methanol (0°, 5 days). After removal of solvents unreacted **6a** was separated from **9a** by column chromatography on silicagel; **9a** was eluted with CH_2Cl_2 - AcOEt (6 : 1), yield 21%, m. p. 45-48° (AcOEt - hexane), $[\alpha]_D$ -19.9° (c 1.0, MeOH); reported $[\alpha]_D$ -17.0° (c=1.89, MeOH).[101]

(*R,R*)-(+)-Tartaric acid diamide (10a)[94]. ^{1}H NMR (CD_3OD) δ 4.43 (s, 2H, CH); ^{13}C NMR (CD_3OD) δ 73.3 (d, J = 145.0 Hz, CH), 177.6 (C=O).

(*R,R*)-(+)-Tartaric acid *N*-methyldiamide (11a). A suspension of 163 mg (1 mmol) **7a** in methanol (2 mL) was stirred at room temperature with 6M $MeNH_2$ in methanol (0.5 mL). After 2 days methanol was partially evaporated and the crystalline product filtered off. Recrystallization from water-methanol afforded **11a**, 115 mg (71%), m. p. 202-204°; ^{1}H NMR (CD_3OD) δ 2.79 (s, 3H, NMe), 4.43 (m, 2H, CH); ^{13}C NMR (CD_3OD - D_2O) δ 26.6 (q, J = 139.0 Hz, NMe), 73.2 (d, J = 145.3 Hz, CH), 174.7 and 177.6 (C=O); IR (KBr) 3380, 3140 (OH and NH), 1673, 1643, 1634 (C=O) cm^{-1}; $[\alpha]^{20}_D$ +126.0° (c 1.0, H_2O). Anal. Calcd. for $C_5H_{10}N_2O_4$: C, 37.04; H, 6.22; N, 17.28. Found: C, 36.84; H, 6.22; N, 16.85.

(*R,R*)-(+)-Tartaric acid *N,N*-dimethyldiamide (12a). A suspension of **7a** (163 mg, 1 mmol) in methanol (2 mL) was stirred at room temperature with 7.2 M Me_2NH in methanol (0.5 mL). After 3 days methanol was evaporated and the residue crystallized from methanol - AcOEt. Product **12a** was obtained as needles, yield 130 mg (74%), m. p. 145-148°; ^{1}H NMR (CD_3OD) δ 2.98 and 3.12 (two s, 6H, NMe_2), 4.26 (d, J = 2.2 Hz, 1H, CH), 4.85 (d, J = 2.2 Hz, 1H, CH); ^{13}C NMR (CD_3OD) δ 36.3 (q, J = 138.4 Hz, NMe), 37.2 (q, J = 138.2 Hz, NMe), 70.6 (d, J = 147.4 Hz, CH), 73.1 (d, J = 143.2 Hz, CH), 172.9 and 177.0 (C=O); IR (KBr) 3390, 3250 (OH and NH), 1685, 1630 (C=O) cm^{-1}; $[\alpha]^{20}_D$ +29.0° (c 1.0, MeOH). Anal. Calcd. for $C_6H_{12}N_2O_4 \cdot H_2O$: C, 37.11; H, 7.27; N, 14.43. Found: C, 37.31; H, 7.24; N, 14.11.

(*R,R*)-(+)-Tartaric acid *N,N'*-dimethyldiamide (13a). The reaction was carried out as described,[94,95] using excess 6M $MeNH_2$ in methanol; yield 81%, m. p. 198-200° (from methanol); ^{1}H NMR (CD_3OD) δ 2.79 (s, 6H, NMe), 4.45 (s, 2H, CH); ^{13}C NMR (CD_3OD) δ 26.1 (q, J = 138.0 Hz, NMe), 74.0 (d, J = 144.9 Hz, CH), 174.9 (C=O); IR (KBr) 3475, 3350, 3320, 3210 (OH and NH), 1650, 1637 (C=O) cm^{-1}; $[\alpha]^{20}_D$ +138.1° (c 1.0, H_2O). Anal. Calcd. for $C_6H_{12}N_2O_4$: C, 40.91; H, 6.87; N, 15.90. Found: C, 40.95; H, 6.78; N, 15.76.

(*R,R*-(+)-Tartaric acid *N,N,N'*-trimethyldiamide (14a). A solution of 435 mg (3 mmol) (+)-*N*-methyltartrimide (**22**)[98], $[\alpha]^{20}_D$ +200° (c 1.0, H_2O), in THF (9 mL) was stirred at room temp. with 7.2 M Me_2NH in THF (1.5 mL). Reaction progress was monitored by polarimetry. After 7 days the initial rotation of the solution, α_D = 8°, decreased to α_D = 2°. The solvents were evaporated *in vacuo* and the oily residue purified by column chromatography on silicagel (solvent CH_2Cl_2 - 5% methanol). Diamide **14a** was obtained as thick oil, yield 480 mg (84%); ^{1}H NMR (CD_3OD) δ 2.79, 2.98 and 3.12 (three s, 9H, NMe), 4.26 (d, J = 2.2 Hz, 1H, CH), 4.84 (d, J = 2.2 Hz, 1H, CH); ^{13}C NMR (CD_3OD) δ 26.1 (q, J = 138.0 Hz, NMe), 36.3 (q, J = 138.1 Hz, NMe), 37.2 (q, J = 138.6 Hz, NMe), 70.7 (d, J = 147.2 Hz, CH), 73.2 (d, J = 143.2 Hz, CH), 173.0 and 174.4 (C=O); IR (film) 3320 (OH and NH), 1660, 1630 (C=O) cm^{-1}; $[\alpha]^{20}_D$ +38.3° (c 1.0, MeOH). Exact mass for $C_7H_{14}N_2O_4$ (M^+ + H): calcd 191.1032; Found 191.1032.

(*R,R*)-(+)-Tartaric acid *N,N,N',N'*-tetramethyldiamide (15a). ^{1}H NMR (CD_3OD) δ 2.91 and 3.18 (two s, 6H, NMe_2), 4.62 (s, 1H, CH); ^{13}C NMR (CD_3OD) δ 35.9 (q, J = 138.2 Hz, NMe), 37.4 (q, J = 138.5 Hz, NMe), 71.2 (dd, J = 146.9 Hz and 4.2 Hz, CH), 173.1 (C=O).

General procedures for preparation of *O,O'*-dibenzoyl derivatives.
Procedure A: 1 mmol diol, benzoyl chloride (0.3 mL) and pyridine (0.2 mL) in CH_2Cl_2 (1 mL) were stirred overnight, then acetone (2 mL) and water (0.2 mL) were added and the mixture was stirred for 1 h at room temp. The product was filtered off or extracted with ethyl acetate and washed with 2N HCl and sat. sodium carbonate, then purified by column chromatography on silicagel (solvent CH_2Cl_2).
Procedure B: 1 mmol diol in cold 2N NaOH (1.5 mL) was shaken with benzoyl chloride (0.4 mL). The product was filtered off, washed with diluted ethanol and crystallized.

(*R,R*)-(-)-*O,O'*-Dibenzoyltartaric acid (1b).[99] ^{1}H NMR ($CDCl_3$) δ 5.99 (s, 2H, CH), 7.35-7.60 (m, 6H, Ph), 8.0-8.1 (m, 4H, Ph); ^{13}C NMR (CD_2Cl_2) δ 71.4 (d, J = 151.7 Hz, CH), 128.7, 128.8, 130.1 and 134.1 (Ph), 165.4 and 170.3 (C=O); UV (dioxane) ε 25600 (230.5 nm).

Monomethyl (*R,R*)-(-)-*O,O'*-Dibenzoyltartrate (2b).[91] ^{1}H NMR (CD_3OD) δ 3.76 (s, 3H, OMe), 5.98 (d, J = 2.9 Hz, 1H, CH), 6.02 (d, J = 2.9 Hz, 1H, CH), 7.5-7.7 (m, 6H, Ph), 8.05-8.15 (m, 4H, Ph); ^{13}C NMR (CD_2Cl_2) δ 53.0 (q, J = 148.1 Hz, OMe), 71.4 (d, J = 151.2 Hz, CH), 71.7 (d, J = 152.3 Hz, CH), 128.8, 130.1 and 134.1 (Ph), 165.3, 166.5 and 169.7 (C=O); UV (dioxane) ε 23800 (230.5 nm).

(*R,R*)-(-)-*O,O'*-Dibenzoyltartaric acid monoamide (3b). A solution of 6.8 g (20 mmol) of anhydride **20** in dioxane (40 mL) was saturated at 0° with gaseous NH_3. Precipitated ammonium salt of **3b** was collected and crystallized from methanol, yield 5.9 g (79%), m. p. 128-133°. The above salt (4.9 g) was dissolved in water and the solution acidified with 2N HCl. The product was filtered off and dried at room temp. to give **3b** as a hydrate, m. p. 107-110°, remelts at 149-157°, yield 4.5 g (92%). Water-free **3b** is obtained by drying at 100°, m. p. 158-162°; ^{1}H NMR (CD_3OD) δ 5.92 (d, J = 2.7 Hz, 1H, CH), 5.96 (d, J = 2.7 Hz, 1H, CH), 7.4-7.7 (m, 6H, Ph), 8.0-8.2 (m, 4H, Ph); ^{13}C NMR (CD_3OD) δ 73.3 (d, J = 150.9 Hz, CH), 74.2 (d, J = 151.7 Hz, CH), 129.5, 130.1, 130,3, 130.8, 130.9, 134.6 and 134.7 (Ph), 166.5, 166.6, 169.4 and 170.7 (C=O); IR (KBr) 3600-2600, 3390, 3200, 1732, 1670, 1655 cm^{-1}; $[\alpha]^{20}_D$ -142.8 (c 1.0, MeOH); UV (dioxane) ε 23500 (230 nm). Anal. Calcd for $C_{18}H_{15}NO_7$: C, 60.51; H, 4.23; N, 3.92. Found: C, 60.11; H, 4.19; N 3.74.

(*R,R*)-(-)-*O,O'*-Dibenzoyltartaric acid mono(*N*-methylamide) (4b). To a solution of anhydride **20** (0.68 g, 2 mmol) in dioxane (4 mL) was added at 0° 5.5 M $MeNH_2$ in THF (1.5 mL). After 15 min. precipitated *N*-methylammonium salt of **4b** was collected (0.78 g, m.p. 171-175°) and recrystallized from methanol - diethyl ether (0.66 g, m. p. 176-181°). The salt was dissolved in water and the solution acidified with 2N HCl to give

4b, 0.61 g, m. p. 112-118°, crystallized from ethanol, yield 0.51 g (69%), m.p. 124-132° (dec.); ^{1}H NMR (dioxane-d_8) δ 2.71 (d, J = 4.7 Hz, 3H, NMe), 5.93 (d, J = 2.8 Hz, 1H, CH), 5.95 (d, J = 2.8 Hz, 1H, CH), 7.06 (q, J = 4.7 Hz, 1H, NH), 7.40-7.65 (m, 6H, Ph), 8.0-8.15 (m, 4H, Ph); ^{13}C NMR (dioxane-d_8) δ 26.8 (q, J = 138.0 Hz, NMe), 73.7 (d, J = 152.4 Hz, CH), 74.9 (d, J = 151.5 Hz, CH), 128.9 130.4, 131.1, 132.5, 133.8 and 135.9 (Ph), 166.2, 167.0 and 169.0 (C=O); IR (KBr) 3510, 3400, 3000-2400, 1736, 1713, 1676 cm^{-1}; $[\alpha]^{20}_D$ -120.6° (c 1.0, dioxane); UV (dioxane) ε 23300 (230.5 nm). Anal. Calcd for $C_{19}H_{17}NO_7$: C, 61.45; H, 4.61; N, 3.77. Found: C, 61.04; H, 4.53; N, 3.73.

(*R,R*)-(-)-*O,O'*-Dibenzoyltartaric acid mono(*N,N*-dimethylamide) (5b). To a suspension of anhydride **18** (3.4 g, 10 mmol) in CH_2Cl_2 (40mL) was added at 0° 7.8 M Me_2NH in 1,2-dimethoxyethane (1.8 mL). After 30 min. the solution was filtered through a short column of silicagel and **5b** eluted with CH_2Cl_2. The product was crystallized from methanol-diethyl ether, yield 2.2 g (57%), m. p. 153-156°; ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 3H, NMe), 3.16 (s, 3H, NMe), 5.94 (d, J = 5.6 Hz, 1H, CH), 6.18 (d, J = 5.6 Hz, 1H, CH), 7.35-7.55 (m, 6H, Ph), 7.95-8.10 (m, 4H, Ph), 8.53 (br s, 1H, COOH); ^{13}C NMR (CD_2Cl_2) δ 36.7 (q, J = 139.8 Hz, NMe), 37.6 (q, J = 138.6 Hz, NMe), 69.1 (d, J = 149.7 Hz, CH), 71.3 (d, J = 150.1 Hz, CH), 128.7, 128.8, 130.1, 130.2, 134.0 and 134.1 (Ph), 165.4, 166.3 and 168.9 (C=O); IR (KBr) 3500-2400, 1757, 1731, 1631 cm^{-1}; $[\alpha]^{20}_D$ - 45.3° (c 1.0, $CHCl_3$); UV (dioxane) ε 27400 (230.5 nm). Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.11; H, 4.79; N, 3.58.

Dimethyl (*R,R*)-(-)-*O,O'*)-Dibenzoyltartrate (6b). From **6a** (procedure A). Yield 83%, m. p. 131-134° (MeOH) (lit.[99] m.p. 132°); ^{1}H NMR ($CDCl_3$) δ 3.77 (s, 3H, OMe), 6.00 (s, 1H, CH), 7.35-7.70 (m, 6H, Ph), 8.0-8.2 (m, 4H, Ph); ^{13}C NMR (CD_2Cl_2) δ 53.4 (q, J = 148.3 Hz, OMe), 71.9 (d, J = 151.9 Hz, CH), 129.1, 130.4 and 134.2 (Ph), 165.5 and 166.8 (C=O); IR (KBr) 1735, 1725 cm^{-1}; $[\alpha]^{20}_D$ -76.5° (c 1.0, $CHCl_3$); UV (dioxane) ε 25500 (231 nm). Anal. Calcd for $C_{20}H_{18}O_8$: C, 62.18; H, 4.70. Found: C, 62.01; H, 4.69.

(*R, R*)-(-)-*O,O'*-Dibenzoyltartaric acid monoamide monomethylester (7b).

A. From **7a** (procedure A). Yield 59%, m. p. 123-126°; ^{1}H NMR (CD_3OD) δ 3.72 (s, 3H, OMe), 5.93 (d, J = 2.8 Hz, 1H, CH), 5.95 (d, J = 2.8 Hz, 1H, CH), 7.45 - 7.7 (m, 6H, Ph), 8.05-8.15 (m, 4H, Ph); ^{13}C NMR (CD_3OD) δ 53.4 (q, J = 148.0 Hz, OMe), 73.3 (d, J = 152.3 Hz, CH), 73.9 (d, J = 151.6 Hz, CH), 129.6, 130.9 and 134.9 (Ph), 166.4, 168.3 and 170.3 (C=O); IR (KBr) 3475, 3240, 1755, 1730, 1700, 1685 cm^{-1}; $[\alpha]^{20}_D$ -133.6° (c 1.0, $CHCl_3$); UV (dioxane) ε 23700 (231 nm). Anal. Calcd for $C_{19}H_{17}NO_7$: C, 61.45; H, 4.61; N, 3.77. Found: C, 61.43; H, 4.55; N, 3.72.

B. From monoamide **3b**. **3b** (100 mg) in methanol (3 mL) was methylated with excess ethereal diazomethane to give **7b**, quantitative yield, crystallized from diethyl ether, m. p. 122-125°.

(*R,R*)-(-)-*O,O'*-Dibenzoyltartaric acid mono(*N*-methylamide) monomethylester (8b). A solution of monoamide **4b** (100 mg) in methanol (5 mL) was methylated with excess ethereal diazomethane. The solution was evaporated and product **8b** was purified by column chromatography on silicagel (solvent CH_2Cl_2), yield 72%, m. p. 174-177° (AcOEt -hexane); ^{1}H NMR ($CDCl_3$) δ 2.84 (d, J = 4.9 Hz, 3H, NMe), 3.72 (s, 3H, OMe), 5.99 (d, J = 2.6 Hz, 1H, CH), 6.10 (d, J = 2.6 Hz, 1H, CH), 6.3 (br s, 1H, NH), 7.35-7.70 (m, 6H, Ph), 8.00-8.15 (m, 4H, Ph); ^{13}C NMR (CD_2Cl_2) δ 26.4 (q, J = 139.1, NMe), 53.2 (q, J = 148.0 Hz, OMe), 72.3 (d, J = 152.9 Hz, CH), 73.1 (J = 152.4 Hz, CH), 128.7, 128.8, 129.0, 129.9, 130.1, 133.9 and 134.3 (Ph), 164.8, 165.2, 166.1 and 167.4 (C=O); IR (KBr) 3390, 1732, 1689, 1669 cm^{-1}; $[\alpha]^{20}_D$ -120.0° (c 1.0, $CHCl_3$); UV (dioxane) ε 24300 (231 nm). Anal. Calcd for $C_{19}H_{17}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.62; H, 4.88; N, 3.62.

(*R,R*)-(-)-*O,O'*-Dibenzoyltartaric acid mono(*N,N*-dimethylamide) monomethylester (9b). A solution of monoamide **5b** (100 mg) in methanol (5 mL) was methylated with excess ethereal diazomethane. The solution

was evaporated and product **9b** was purified by column chromatography on silicagel (solvent CH_2Cl_2), yield 66%, m. p. 95-103° (MeOH-Et_2O); ^1H NMR ($CDCl_3$) δ 2.98 (s, 3H, NMe), 3.21 (s, 3H, NMe), 3.79 (s, 3H, OMe), 6.00 (d, J = 5.2 Hz, 1H, CH), 6.22 (d, J = 5.2 Hz, 1H, CH), 7.3-7.7(m, 6H, Ph), 8.00-8.15 (m, 4H, Ph); ^{13}C NMR (CD_2Cl_2) δ 36.3 (q, J = 138.0 Hz, NMe), 37.2 (q, J = 136.6 Hz, NMe), 53.2 (q, J = 148.0 Hz, OMe), 70.2 (d, J = 151.3 Hz, CH), 71.0 (d, J = 151.2 Hz, CH), 128.8, 129.1, 130.0 and 133.9 (Ph); $[\alpha]^{20}_D$ -9.2° (c 1.0, $CHCl_3$); UV (dioxane) ε 26000 (231 nm). Anal. Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 63.00; H, 5.28; N, 3.50.

(*R,R*)-(-)-*O,O'*-Dibenzoyltartaric acid diamide (10b). From **10a** (procedure B). Yield 62%, m. p. 252-255° (ethanol); ^1H NMR (C_5D_5N) δ 5.09 (s, 2H, CH), 7.25-7.55 (m, 6H, Ph), 8.3-8.4 (m, 4H, Ph), 9.0 (br s, 4H, NH_2); ^{13}C NMR (CD_3OD) δ 74.4 (d, J = 151.3 Hz, CH), 129.5, 131.0 and 134.7 (C=O), 166.6 and 171.0 (C=O); IR (KBr) 3400, 3240, 1730, 1686 cm^{-1}; $[\alpha]_D$ -165.4° (c 1.0, MeOH); UV (dioxane) ε 23800 (231 nm). Anal. Calcd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.56; H, 4.55; N, 7.74.

(*R,R*)-(-)-*O,O'*-Dibenzoyltartaric acid *N*-methyldiamide (11b). To a solution of DCC (227mg, 1 mmol) in THF (8 mL) was added at 0° **4b** (371 mg, 1 mmol), followed by 5.5 M $MeNH_2$ in THF (0.3 mL). After stirring at room temp. overnight dicyclohexylurea (0.2 g) was filtered off and the solution evaporated to dryness. The crude product was purified by column chromatography on silicagel (solvent 1% MeOH in CH_2Cl_2) and crystallized from methanol - diethyl ether. Yield 32%, m. p. 206-208°; ^1H NMR (CD_3OD) δ 2.69 (s, 3H, NMe), 5.90 (d, J = 2.8 Hz, 1H, CH), 5.92 (d, J = 2.8 Hz, 1H, CH), 7.45-7.65 (m, 6H, Ph), 8.1-8.2 (m, 4H, Ph); ^{13}C NMR (CD_3OD) δ 26.5 (q, J = 138.5 Hz, NMe), 74.4 (d, J = 151.1 Hz, CH), 74.7 (d, J = 151.8 Hz, CH), 129.5, 129.6, 130.1, 130.9, 131.0 and 134.7 (Ph), 166.4, 166.6, 169.0 and 170.9 (C=O); IR (KBr) 3420, 3295, 1725, 1700, 1665 cm^{-1}; $[\alpha]^{20}_D$ -147.5° (c 1.0, MeOH); UV (dioxane) ε 24100 (230 nm). Anal. Calcd for $C_{19}H_{18}N_2O_6$: C, 61.62; H, 4.90; N, 7.56. Found: C, 61.59; H, 4.85; N, 7.63.

(*R,R*)-(-)-*O,O'*-Dibenzoyltartaric acid *N,N*-dimethyldiamide (12b). To a solution of DCC (227 mg, 1 mmol) in THF (8 mL) was added at 0° **5b** (385 mg, 1 mmol), followed by 1.5 M NH_3 in THF (1 mL). After stirring at room temp. overnight dicyclohexylurea (0.2 g) was filtered off and the solution evaporated to dryness. The residue was subjected to column chromatography on silicagel. **12b** was eluted with 1% MeOH in CH_2Cl_2, yield 120 mg (31%), m. p. 152-154° (MeOH - Et_2O); ^1H NMR ($CDCl_3$) δ 2.95 (s, 3H, NMe), 3.25 (s,3H, NMe), 5.9 (br s, 1H, NH), 6.01 (d, J = 5.8 Hz, 1H, CH), 6.29 (d, J = 5.8 Hz, 1H, CH), 6.5 (br s, 1H, NH), 7.35-7.55 (m, 6H, Ph), 8.0-8.1 (m, 4H, Ph); ^{13}C NMR (CD_2Cl_2) δ 36.2 (q, J = 138.5 Hz, NMe), 37.3 (q, J = 138.0 Hz, NMe), 70.0 (d, J = 152.3 Hz, CH), 72.1 (d, J = 151.2 Hz, CH), 128.7, 128.8, 130.0, 130.1, 133.7 and 133.9 (Ph), 165.3, 165.5, 165.8 and 168.8 (C=O); IR (KBr) 3610, 3460, 3335, 1725, 1690, 1650 cm^{-1}; $[\alpha]^{20}_D$ -28.6° (c 1.0, $CHCl_3$); UV (dioxane) ε 25500 (230 nm). Anal. Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.32; H, 5.23; N, 7.28.

(*R,R*)-(-)-*O,O'*-Dibenzoyltartaric acid *N,N'*-dimethyldiamide (13b). From **13a** (procedure B). Yield 67%, m. p. 267-269° (DMF-AcOEt); ^1H NMR (C_5D_5N) δ 2.87 (d, J = 4.7 Hz, 6H, NMe), 5.41 (s, 2H, CH), 7.2-7.5 (m, 6H, Ph), 8.20-8.35 (m, 4H, Ph), 9.4 (br s, 2H, NH); ^{13}C NMR (C_5D_5N) 26.5 (q, J = 137.2 Hz, NMe), 75.0 (d, J = 150.8 Hz, CH), 128.8, 130.0, 130.3 and 133.7 (Ph), 166.0 and 167.5 (C=O); IR (KBr) 3365, 1732, 1660 cm^{-1}; $[\alpha]^{20}_D$ -158.0° (c 1.0, DMF); UV (dioxane) ε 24200 (230 nm). Anal. Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.08; H, 5.03; N, 7.60.

(*R,R*)-(-)-*O,O'*-Dibenzoyltartaric acid *N,N,N'*-trimethyldiamide (14b). The procedure for the preparation of **12b** was followed except that 5.5 M $MeNH_2$ in THF (0.4 mL) was used instead of NH_3 solution. Yield 33%, m. p. 201-203° (ethanol); ^1H NMR (dioxane-d_8) δ 2.4 (br s, 1H, NH), 2.71 (d, J = 4.7 Hz, 3H, NMe), 2.83 (s,

3H, NMe), 3.18 (s, 3H, NMe), 5.83 (d, J = 6.0 Hz, CH), 6.18 (d, J = 6.0 Hz, CH), 7.3 - 7.6 (m, 6H, Ph), 7.9-8.1 (m, 4H, Ph); ^{13}C NMR (CD_2Cl_2) δ 26.5 (q, J = 138.5 Hz, NMe), 36.2 (q, J = 138.5 Hz, NMe), 37.4 (q, J = 138.5 Hz, NMe), 70.0 (d, J = 150.0 Hz, CH), 72.7 (d, J = 149.8 Hz, CH), 128.8, 128.9, 129.2, 129.5, 130.0, 130.2, 133.7 and 134.0 (Ph), 165.5, 165.6, 166.0 and 166.8 (C=O); IR (KBr) 3400, 1720, 1670 cm^{-1}; $[\alpha]^{20}_D$ -15.2° (c 1.0, $CHCl_3$); UV (dioxane) ε 26500 (230.5 nm). Anal. Calcd for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.20; H, 5.71; N, 7.18.

(*R,R*)-(+)-*O,O'*-Dibenzoyltartaric acid *N,N,N',N'*-tetramethyldiamide (15b). From **15a** (procedure A). Yield 89%, m. p. 190-192° (AcOEt); ^{1}H NMR ($CDCl_3$) δ 2.98 (s, 6H, NMe), 3.25 (s, 6H, NMe), 6.43 (s, 2H, CH), 7.3-7.5 (m, 6H, Ph), 7.9-8.0 (m, 4H, Ph); ^{13}C NMR (CD_2Cl_2) δ 36.0 (q, J = 138.4 Hz, NMe), 36.7 (q, J = 138.5 Hz, NMe), 70.1 (dd, J = 154.6 Hz, 5.8 Hz, CH), 128.6, 129.0, 129.9 and 133.6 (Ph), 165.6 and 166.7 (C=O). $[\alpha]^{20}_D$ +108.0° (c 1.0, $CHCl_3$); UV (dioxane) ε 28900 (230 nm). Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 64.01; H, 5.86; N, 6.67.

Methyl (2*R*,3*S*)-2,3-dibenzoyloxy-3-cyanopropanoate (16). Monoamide **7a** (163 mg, 1 mmol) was dissolved in pyridine (0.7 mL) and stirred at room temp. with benzoyl chloride (0.4 mL) for 24 h. Reaction products were separated by extraction with CH_2Cl_2 and 2n HCl followed by sat. Na_2CO_3 and purified by column chromatography on silicagel (solvent CH_2Cl_2). Nitrile **16** was obtained as oil, yield 245 mg (69%); ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H, OMe), 5.84 (d, J = 3.6 Hz, 1H, CH), 6.21 (d, J = 3.6 Hz, 1H, CH), 7.45-7.70 (m, 6H, Ph), 8.0-8.2 (m, 4H, Ph); ^{13}C NMR (CD_2Cl_2) δ 53.7 (q, J = 148.5 Hz, OMe), 61.4 (d, J = 157.6 Hz, CH), 70.9 (d, J = 152.7 Hz, CH), 113.9 (C≡N), 127.7, 128.4, 128.9, 129.0, 130.1, 130.3, 134.4 and 134.7 (Ph), 164.3, 165.0 and 165.3 (C=O); IR (film) 1760, 1730 cm^{-1}; $[\alpha]^{20}_D$ -36.6° (c 1.0, $CHCl_3$); UV (dioxane) ε 25200 (232 nm). Anal. Calcd for $C_{19}H_{15}NO_6$: C, 64.59; H, 4.28; N, 3.96. Found: C, 64.21; H, 4.10; N, 3.95.

***N*-Methyl (2*R*,3*S*)-2,3-dibenzoyloxy-3-cyanopropanamide (17).** Reaction was carried-out as for **16**, using 162 mg (1 mmol) diamide **11a**. Nitrile **17** was obtained as crystals, m. p. 137-139° (Et_2O), yield 235 mg (66%); ^{1}H NMR ($CDCl_3$) δ 2.85 (d, J = 4.9 Hz, 3H, NMe), 5.97 (d, J = 3.9 Hz, 1H, CH), 6.22 (d, J = 3.9 Hz, 1H, CH), 6.5 (br s, 1H, NH), 7.3-7.7 (m, 6H, Ph), 8.0-8.2 (m, 4H, Ph); ^{13}C NMR (CD_2Cl_2) δ 26.6 (q, J = 139.4 Hz, NMe), 61.8 (d, J = 158.7 Hz, CH), 72.0 (dd, J = 152.4 Hz, 2.5 Hz, CH), 114.6 (C N), 128.1, 128.2, 129.0, 129.1, 130.2, 130.4, 134.5 and 134.7 (Ph), 164.4 and 164.8 (C=O); $[\alpha]^{20}_D$ - 69.5° (c 1.0, $CHCl_3$); IR (KBr) 3300, 1745, 1730, 1660 cm^{-1}; UV (dioxane) ε 24400 (232 nm). Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.49; H, 4.38; N, 7.80.

***N,N*-Dimethyl (2*R*,3*S*)-2,3-dibenzoyloxy-3-cyanopropanamide (18).** Reaction was carried-out as for **16**, using 176 mg (1 mmol) diamide **12a**. Nitrile **18** was obtained as crystals, m. p. 99-101° (Et_2O), yield 220 mg (60%); ^{1}H NMR ($CDCl_3$) δ 3.07 (s, 3H, NMe), 3.21 (s, 3H, NMe), 6.20 (d, J = 8.2 Hz, 1H, CH), 6.26 (d, J = 8.2 Hz, 1H, CH), 7.35-7.60 (m, 6H, Ph), 7.90-8.05 (m, 4H, Ph); ^{13}C NMR (CD_2Cl_2) δ 36.3 (q, J = 138.9 Hz, NMe), 37.4 (q, J = 138.4 Hz, NMe), 61.4 (dd, J = 161.1 Hz, 5.0 Hz, CH), 68.3 (dd, J = 152.2 Hz, 6.0 Hz, CH), 114.6 (C≡N), 128.0, 128.3, 128.9, 130.2, 134.3 and 134.4 (Ph), 164.4, 164.5 and 165.1 (C=O); IR (KBr) 1735, 1720, 1680 cm^{-1}; $[\alpha]^{20}_D$ + 87.5° (c 1.0, $CHCl_3$); UV (dioxane) ε 25800 (232 nm). Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.32; H, 4.94; N, 7.60.

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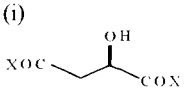
55. For compounds with double - sign Cotton effect the weighed experimental value is compared with the calculated one. The validity of the analysis of the CD data is supported by additional CD measurements on the derivatives of (R)-malic acid (i)



(i)

X = OH, Δε -0.8 (209 nm); X = OMe, Δε -0.8 (210 nm); X = NH_2, Δε +1.0 (211 nm); X = NHMe, Δε +1.8 (208 nm); X = NMe_2, Δε -2.5 (202 nm) in water solution. As expected, the Cotton effects are of the same sign but roughly half the magnitude of the Cotton effects of the corresponding (R,R)-tartaric acid derivatives. This implies that C_α stereogenic center is the primarily factor responsible for the generation of the n-π* Cotton effect.
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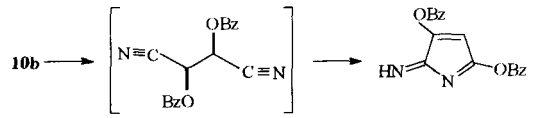
59. The second maximum of the exciton Cotton effect at shorter wavelengths is not observed in a number of cases shown in Table 1, probably as a result of cancelling or overlapping by Cotton effects due to other transitions.
60. As representative A values for *T* and *G*⁻ conformers we use -35.0 and +21.8, respectively. The former amplitude is the average value for **1b**, **6b** and **10b** (see ref. 59) while the latter is that of **15b**.
61. Attempted preparation of dinitrile of *O,O'*-dibenzoyltartaric acid (**23**) by dehydration of diamide **10b** with DMF-$(COCl)_2$ or DMF-$SOCl_2$-NEt_3 resulted in the formation of **24**, most probably via intramolecular benzoyloxy group transfer and cyclization of the dinitrile.



24: prisms, m. p. 192-4° (ethyl acetate-hexane); ^{1}H NMR (C_5D_5N) δ 7.20 (s, 1H), 7.3-8.5 (m, 10H), 13.6 (s, 1H); IR (KBr) 2950, 2930, 1745, 1600, 1455, 1305, 1240, 1085, 1065, 1025, 720, 700 cm^{-1}; MS: 320 (M^+), 105 ($PhCO^+$), 77 (Ph^+). Anal. Calcd for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75; Found: C, 67.21; H, 3.77; N, 8.70.

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