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Study of the Diastereoisomers Formed between (N-alkyl)-pipecolic acid-anilides and 2R,3R-tartaric acid or O,O'-dibenzoyl-2R,3R-tartaric acid. Do the Tartaric Acids Form Molecular-Complexes, instead of Salts During Optical Resolutions?

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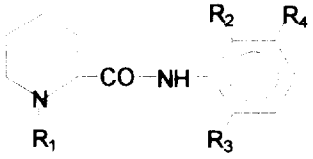
Abstract: It was found that during the optical resolution of (N-alkyl)-pipecolic acid-anilides by 2R,3R-tartaric acid and O,O'-dibenzoyl-2R,3R-tartaric acid that the precipitated diastereoisomer was not the salt but a diastereoisomeric complex in 8 cases from 13. The results indicate that tartaric acids may be used as general resolving agents for optical resolution of racemates even having no basic group.

The 2R,3R-tartaric acid (furthermore TA) and the O,O'-dibenzoyl-2R,3R-tartaric acid (furthermore DBTA) are the two most widely applied resolving agents for resolution of racemic bases via diastereoisomeric salt formation.[1,2] Recently it was reported that the trans-bicyclo[2.2.1]heptane-2,3-diamine can be resolved with DBTA by complex formation.[3]

During optical resolution of racemic bases by acidic resolving agents it was always assumed that the process take place by diastereoisomeric salt formation. In the light of the paper of Hatamo et.al.[3] we decided to investigate weather the complex formation is a rare exception or a common thing during optical resolution by DBTA or TA. For model resolution we selected the optical resolution of some (N-alkyl)-pipecolic acid-anilides **1a-1m**[4] by DBTA and TA.



1	a	b	c	d	e	f	g	h	i	j	k	l	m
R_1	H	CH_3	C_2H_5	C_3H_7	C_4H_9	H	C_2H_5	C_3H_7	C_4H_9	H	C_2H_5	C_3H_7	C_4H_9
R_2	CH_3	CH_3	CH_3	CH_3	CH_3	H	H	H	H	H	H	H	H
R_3	CH_3	CH_3	CH_3	CH_3	CH_3	H	H	H	H	H	H	H	H
R_4	H	H	H	H	H	H	H	H	H	CF_3	CF_3	CF_3	CF_3

[○] deceased

Our model bases can be classified into three subgroups (N-alkyl)-pipecolic acid-anilides (**1f-1i**); (N-alkyl)-pipecolic acid-2,6-dimethyl-anilides (**1a-1e**) and (N-alkyl)-pipecolic acid-3-trifluoromethyl-anilides (**1j-m**). The preparation of the racemic anilides and 2,6-dimethyl-anilides (**1a-1i**) were already known, while the 3-trifluoromethyl-anilides were synthetized by us. The synthesis of pipecolinic acid 3-trifluoromethyl-anilides **1j-m** has been performed similarly to the synthesis of the unsubstitued anilides.[5,6] 3-Trifluoromethyl-aniline was acylated with picolinic acid by means of phosphoryl-chloride condensing agent. The anilides were catalyically hydrogenated to the pipecolinic acid anilides, which were alkylated by means of alkyl-bromides.

Table 1. Summary of the optical resolutions

	R_1	molar ratio base:acid	Resolving agent	Solvent	Yield of precipitate %	$[\alpha]_D^{20}$ of base	Opt. purity of base %	
1a	H	2:1	DBTA	i-PrOH	75.4	+43.2[d]	94	salt
1b	Me	1:1	DBTA	EtOH	93.3	-63.0[e]	99	complex
1c	Et	2:1	DBTA	i-PrOH	63.4	+51.2[f]	73	salt
1d	n-Pr	1:1	TA	EtOHaq[a]	93.4	+77.0[e]	95	complex
1e	n-Bu	2:1	TA	i-PrOH	68.4	+84.0[e]	100	salt
1f	H	2:1	TA	EtOHaq[b]	67.5	+1.5[e]	10	salt
1g	Et	1:1	DBTA	i-PrOH	50.0	-120.4[e]	77	complex
1h	n-Pr	1:1	DBTA	i-PrOH	42.0	-102.6[e]	95	complex
1i	n-Bu	1:1	TA	EtOHaq[b]	54.8	-26.0[e]	?	complex
1j	H	2:1	TA	EtOH	65.2	+ 1.7[e]	15	salt
1k	Et	1:1	DBTA	i-PrOH	66.8	-56.6[e]	91	complex
1l	n-Pr	1:1	DBTA	EtOH	58.5	-64.0[e]	80	complex
1m	n-Bu	1:1	TA	EtOHaq[c]	41.6	-62.4[e]	78	complex

EtOHaq= [a]96% EtOH; [b]EtOH: water 3:1; [c]EtOH: water 3:1; $[\alpha]_D^{20}$ measured in [d](c:2.3; 1NHCl); [e](c:1; MeOH); [f](c:2; EtOH)
The molar ratio of the molecules in the precipitated diastereoisomers were determined from the ratio of the methyne protons of the resolving acid and either the aromatic or the methyl protons of the base in the NMR-spectra. The optical purity of the base were calculated from the specific rotation of the base liberated from the precipitated diastereoisomer.

The optical resolution of all the bases were accomplished by either DBTA or TA in different alcoholic solutions, the results summarised in Table 1. (The resolutions of **1a,b,c,d,e,g,i** were already known[4a,7]). It is interesting that none of the bases was resolvable by both acids.

The precipitated salts were subjected to IR (for the study of complexation) and ^{1}H-NMR (for the determination of the molar ratio of base:acid) measurements. The IR spectra of only five diastereoisomers exhibited fully ionised carboxylate and ammonium groups as it can expected in case of salt formation. In all the other cases the spectra revealed unionised amino and carboxylic acid groups, without any trace of salt formation, which clearly indicates that diastereoisomeric molecular complexes and not diastereoisomeric salts were formed during the resolution. The ^{1}H-NMR measurements revealed two different stochiometries for the diastereoisomers. 2:1 base:acid ratio when real salt formation was detected, while in every case when complex

formation were found the molar ratio was 1:1. In case of salt formation the diastereoisomeric salts precipitated in 2:1 ratio even when the base and the acid were reacted in 1:1 ratio. We were not able to recognise any relationships between the structure of the bases and the type of the diastereoisomer, except that salts were formed in all the three cases when R_1=H. Complex formation was observed not only in case of DBTA, but also in case of TA. Salts of TA with different chiral bases have been extensively investigated,[8] but complex formation have never been described.

Our results indicate that the complex formation not uncommon during optical resolutions by tartaric acids. We think more examples are just not known, because the salt formation is always assumed, it is usually never checked. Also there is no salt formation in case of optical resolution by "quasi-racemate" formation, when for example the malic acid resolved by TA.[9]

The fact that for an efficient resolution by tartaric acids salt formation is not required, led to the conclusion that not only bases, but other type of racemates, having no basic group may be resolved by tartaric acids. That may have great practical importance, since by that time the racemates having no acidic or basic group resolved indirectly after derivatizing or by complex formation with complicated, usually expensive host compounds. The easily available, inexpensive tartaric acids can be a good alternative of other resolving agents for any kind of racemates.

Experimental

All chemicals were purchased from Merck. With the exception of racemic **1a-1i**, which were supplied by EGIS Pharmaceutical Factory. Melting points were determined on a Büchi 535 apparatus, and are uncorrected. Microanalyses were performed using a Perkin-Elmer 2400 CHN elemental analyzer. IR spectra were recorded with the aid of a Brucker IFS-113 v spectrophotometer in KBr discs. NMR spectra were measured on a Brucker WM-250 spectrometer in $CDCl_3$. Mass spectra were determined on a Kratos 80 mass spectrometer using 70 eV and 150°C. Specific rotations were measured on a Perkin-Elmer 241 polarimeter.

Preparation of picolinic acid trifluoromethyl-anilide:

Phosphoryl chloride (7,6 g, 0,036 mol) was added dropwise under stirring to a mixture of picolinic acid (12,6 g, 0,1 mol), m-trifluoromethyl-aniline (16.1 g, 0,1 mol) and N,N-dimethyl aniline (16.2 g, 0,01 mol) and was stirred under reflux for 4 hours. The reaction mixture was cooled to 85°C, and poured onto 10% hydrochloric acid solution. pH of the solution was adjusted to 2,0-2,5 by 25% sodium hydroxide. The precipitated product was crystallised on 0-5°C for 3 hours, then filtered. Y: 80,5%, m.p.: 105°C

Microanal.: theor.: C: 58,65% H: 3,40% N: 10,53% F: 21, 41%

found: C: 58,83% H: 3,31% N: 10,45% F: 21,48%

Ms: M^+: 266, m/z(rel. int. %): 247 (4,8) $C_{13}H_9N_2OF_2^+$; 237 (4,1) M-29$^+$; 187 (3,9) $(C_6H_4\text{-}CF_3)\text{-}NH\text{-}CO^+$; 106 (30,2) $C_5H_4N\text{-}CO\text{-}NH^+$; 78 (100,0) $C_5H_4N^+$

IR:(cm^{-1}): 3317 (ν-NH); 1682 (amid I); 1545 (amid II); 1232, 1177, 1124 (νCF_3).

^{1}H-NMR: δ(ppm): 10,15 (1H, -NH-); 8,7-7,1 (m, 8H, Ar-H)

The crude product was crystallised from ethanol-water 4 : 3 mixture

Preparation of pipecolinic acid trifluoromethyl-anilide (1j)

Picolinic acid trifluoromethyl-anilide (20.29 g 0,076 mol) was dissolved in 150 cm^3 of methanol and 10% palladium on charcoal catalyst (2,0g) was added in aqueous suspension. The mixture was placed into a hydrogenating autoclave fitted with stirrer. Hydrogenation was led on 50°C, on 5-7 bar until the theoretical amount was absorbed in 22 hours. The catalyst was filtered and washed. The mother liquor was evaporated to its seventh part diluted with water (double volume of the remaining solvent) and let to crystallise.The precipitate was filtered. (Table 2.)

*Preparation of N-alkyl- pipecolinic acid trifluoromethyl- anilides (**1k-m**)(General procedure)*

Pipecolinic acid trifluoromethyl-anilide (17.95 g, 0,066 mol) , potassium carbonate (13,4g; 0,0967 mol), alkyl-bromide (0,00967 mol) and potassium-iodide (1,56g; 0,0094 mol) in methyl isobuthyl ketone (150 cm^3) was stirred under reflux for six hours. The reaction mixture was poured on water (200 cm^3), and the two phases were separated. The upper organic layer was dried on potassium carbonate, then the solvent was evaporated. The residue solidified. For purification it was dissolved in acetone, clarified, filtered and evaporated. (Table 2.)

Table 2. Yields and analytical data of **1j-1m**

Comp.	Yield[a.] (%)	m.p. (°C)	Molecular formula	$M^{+b.}$	theor. / found C	H	N	F
1j	91,2	98-99	$C_{13}H_{15}N_2OF_3$		57,34	5,55	10,29	20,94
			272,27	272	56,93	5,70	9,95	20,54
1k	65,1	69-71	$C_{15}H_{19}N_2OF_3$		59,99	6,37	9,33	18,98
			300,32	300	60,31	6,35	9,40	18,20
1l	58,3	67-69	$C_{16}H_{21}N_2OF_3$		61,13	6,74	8,91	18,13
			314,35	314	62,55	6,47	9,14	17,13
1m	66,2	boil. p. 82-85	$C_{17}H_{23}N_2OF_3$		62,18	7,06	8,53	17,36
			328,37	328	62,67	7,30	8,33	16,91

a., yields of isolated products

b., measured by chemical ionisation

*Preparation of the diastereomers of **1a-m** for IR and NMR measurements (General procedure)*

The hot solution of the racemic base (1 or 2 mol) was added dropwise to the hot alcoholic solution of the resolving acid (1 mol). The transparent solution was left to cool under effective stirring. Under 70°C the crystals started to precipitate. These were filtered, washed with the solvent and dried.

1a-DBTA : IR: (cm^{-1}): 3400-2500 (ν-NH^+); 1721 (νC=O acid); 1629 and 1366 (COO^- carboxylate); 1265 and 1115 (νO=C-O-C benzoate); 767 and 718 (γC_{ar}-H). ^{1}H-NMR: molar ratio = 2 : 1 ; δ(ppm) {J(Hz)}: 8,0 (d (J=6,5), 2H, Ar-H_{ortho}, DBTA); 7,63 (t (J=7,3), 1H, Ar-H_{para}, DBTA); 7,50 (t (J= 7,4), 2H, Ar-H_{meta}, DBTA); 7,04 (dd (J=7,1; 4,5), 3H, Ar-$H_{meta,para}$, base); 5,64 (s, 1H, -CH-, DBTA); 2,09 (s, 6H, 2× -CH_3, xylidide)

1b-DBTA : IR:(cm^{-1}): 3497 -(νNH-); 3246 (νOH carboxylic acid); 1724 (νC=O acid); 1259 and 1094 (ν O=C-O-C benzoate); 775 and 708 (γC_{ar}-H). ^{1}H-NMR: molar ratio = 1 : 1; δ(ppm) {J(Hz)}: 8,0 (m, 4H, Ar-H_{ortho}, DBTA); 7,50 (m, 6H, Ar-$H_{meta,para}$, DBTA); 7,04 (s, 3H, Ar-$H_{meta,para}$, base); 5,70 (s, 2H, -CH-, DBTA); 2,09 (s, 6H, 2× -CH_3, xylidide)

1c-DBTA : IR: (cm^{-1}): 3400-2500 (ν-NH^+); 1715 (νC=O acid); 1626 and 1371 (νCOO$^-$ carboxylate); 1267 and 1121 (νO=C-O-C benzoate); 777 and 719 (γC_{ar}-H). ^{1}H-NMR: molar ratio = 2 : 1 ; δ(ppm) { J(Hz)}: 8,0 (m, 2H, Ar-H_{ortho}, DBTA); 7,55 (m, 3H, Ar-$H_{meta,para}$, DBTA); 7,02 (s, 3H, Ar-$H_{meta,para}$, base); 5,70 (s, 1H, -CH-, DBTA); 2,10 (s, 6H, 2× -CH_3, xylidide)

1d-TA : IR: (cm^{-1}): 3442 (ν-NH); 2969 (carboxylic acid); 1685 (amide I.); 772 (γC_{ar}-H). ^{1}H-NMR: molar ratio = 1 : 1; δ(ppm) {J(Hz)}: 7,26-7,18 (m, 3H, Ar-$H_{meta,para}$, base); 4,47 (s, 2H, -CH-, TA); 2,19 (s, 6H, 2× -CH_3, xylidide)

1e-TA : IR: (cm^{-1}): 3400-2500 (ν-NH^+); 1682 (amide I).; 1629 and 1377 COO$^-$ carboxylate; 766 (γC_{ar}-H).^{1}H-NMR: molar ratio = 2 : 1; δ(ppm) {J(Hz)}: 7,30-7,19 (m, 3H, Ar-$H_{meta,para}$, base); 4,37 (s, 1H, -CH-, TA); 2,20 (s, 6H, 2× -CH_3, xylidide)

1f-TA : IR: (cm^{-1}): 3400-2500 (ν-NH^+); 1658 and 1562 (amide I.- II.); 1625 and 1323 COO$^-$ carboxylate; 769 (γC_{ar}-H). ^{1}H-NMR: molar ratio = 2 : 1; δ(ppm) {J(Hz)}: 7,63 (d (J=7,5), 2H, Ar-H_{ortho}, base); 7,32 (t (J=7,5), 2H, Ar-H_{meta}, base); 7,07 (t (J=7,4), 1H, Ar-H_{para}, base); 3,90 (s, 1H, -CH-, TA)

1g-DBTA : IR: (cm^{-1}): 3327 (ν-NH); 2957 (carboxylic acid); 1720 (νC=O acid); 1684 (amide I.); 1263 and 1117 (νO=C-O-C benzoate); 712 (γC_{ar}-H). ^{1}H-NMR: molar ratio = 1 : 1; δ(ppm) {J(Hz)}: 8,05-7,93 (m, 4H, Ar-H_{ortho}, DBTA); 7,67-7,50 (m, 6H, Ar-H_{meta}, DBTA + Ar-H_{ortho}, base); 7,50-7,0 (m, 5H, Ar-H_{para}, DBTA + Ar-$H_{meta,para}$, base); 1,23 (t (J=7,2), 3H, N-alkyl -CH_3, base). The -CH- signal of DBTA overlaps with the -COOH signal (integral could not be calculated).

1h-DBTA : IR: (cm^{-1}): 3279 (ν-NH); 2949 (carboxylic acid); 1720 (νC=O acid); 1265 and 1109 (νO=C-O-C benzoate); 714 (γC_{ar}-H). ^{1}H-NMR: molar ratio = 1 : 1; δ(ppm) {J(Hz)}: 8,06-7,95 (m, 4H, Ar-H_{ortho}, DBTA); 7,68-7,51 (m, 6H, Ar-H_{meta}, DBTA + Ar-H_{ortho}, base); 7,40-7,15 (m, 5H, Ar-H_{para}, DBTA + Ar-$H_{meta,para}$, base); 5,78 (s, 2H, -CH-, DBTA); 0,78 (t (J=7,2), 3H, N-alkyl -CH_3, base)

1i-TA : IR: (cm^{-1}): 3323 (ν-NH); 1728 (νC=O acid); 1564 (amide II).; 789 (γC_{ar}-H).
^{1}H-NMR: molar ratio = 1 : 1; δ(ppm) {J(Hz)}: 7,62 (d (J=7,3), 2H, Ar-H_{ortho}, base); 7,31-7,18 (m, 3H, Ar-$H_{meta,para}$, base); 4,15 (s, 2H, -CH-, TA); 1,20-1,14 (t (J=7,3), 3H, N-alkyl -CH_3, base)

1j-TA : IR:(cm^{-1}): 3400-2500 (ν-NH^+); 1690 (amide I).; 1609 and 1335 (COO$^-$ carboxylate); 700 (γC_{ar}-H). ^{1}H-NMR: molar ratio = 2 : 1; δ(ppm) {J(Hz)}: 8,14 (s, 1H, C_{2ar}-H, base); 7,88 (d (J=7,5), 1H, C_{5ar}-H, base); 7,57-7,46 (m, 2H, $C_{4,6ar}$-H, base); 4,00 (s, 1H, -CH-, TA)

1k-DBTA : IR: (cm^{-1}): 3528 (ν-NH); 2947 (carboxylic acid), 1724 (νC=O acid); 1697 (amide I.); 1263 and 1123 (νO=C-O-C benzoate); 716 (γC_{ar}-H). ^{1}H-NMR: molar ratio = 1 : 1; δ(ppm) {J(Hz)}: 8,06-7,94 (m, 5H, Ar-H_{ortho}, DBTA + C_{2ar}-H, base); 7,64-7,45 (m, 9H, Ar-$H_{meta,para}$, DBTA + $C_{4,5,6ar}$-H, base); 5,79 (s, 2H, -CH-, DBTA); 1,23-1,07 (t (J=7,0), 3H, N-alkyl -CH_3, base)

1l-DBTA : IR: (cm^{-1}): 3552 (ν-NH); 2965 (carboxylic acid) 1722 (νC=O acid); 1266 and 1123 (νO=C-O-C benzoate); 717 (γC_{ar}-H).^{1}H-NMR: molar ratio = 1 : 1; δ(ppm) {J(Hz)}: 8,15-8,04 (m, 5H, Ar-H_{ortho}, DBTA + C_{2ar}-H, base); 7,67-7,15 (m, 9H, Ar-$H_{meta,para}$, DBTA + $C_{4,5,6ar}$-H, base); 6,00 (s, 2H, -CH-, DBTA); 0,80-0,63 (t (J=7,2), 3H, N-alkyl -CH_3, base)

1m-TA : IR: (cm^{-1}): 3459 (ν-NH); 2965 (carboxylic acid); 1694 and 1573 (amide I.- II.); 698 (γC_{ar}-H). ^{1}H-NMR: molar ratio = 1 : 1; δ(ppm) {J(Hz)}: 8,20 (s, 1H; C_{2ar}-H, base); 7,96 (d (J=7,2), 1H, C_{5ar}-H, base); 7,83-7,70 (m, 2H, $C_{4,6ar}$-H, base); 4,87 (s, 2H, -CH-, TA); 1,20-1,14 (t (J=7,3), 3H, N-alkyl -CH_3, base)

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