Liquid Chromatography on Triacetylcellulose, 14[1]

Chromatographic Separation of Enantiomers and Barriers to Enantiomerization of Axially Chiral Aromatic Carboxamides

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The enantiomers (*M*) and (*P*) of a series of similar aromatic carboxamides have been, for the first time, investigated analytically and enriched preparatively by liquid chromatography on triacetylcellulose. Enantiomeric purities (7–99%), specific rotations, and barriers to rotation about the $C(sp^2)-C(sp^2)$ bond (87–120 kJ/mol, Table 5) were determined. These energies are discussed in terms of the size of *ortho* substituents and of the buttressing effects by *meta* substituents.

Flüssigkeits-Chromatographie an Triacetylcellulose, 14[1]. – Chromatographische Trennung von Enantiomeren und Enantiomerisierungsschwellen axial-chiraler aromatischer Carbonsäureamide

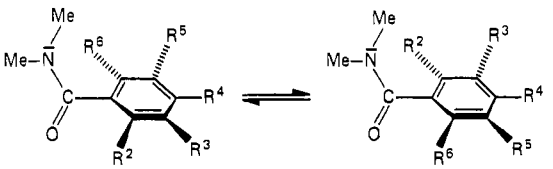
Die Enantiomeren (*M*) und (*P*) einer Reihe verwandter aromatischer Carbonsäureamide wurden erstmals mittels Flüssigkeits-Chromatographie an Triacetylcellulose analytisch untersucht und präparativ angereichert. Enantiomerenreinheiten (7–99%), spezifische Drehungen und Schwellen der Rotation um die $C(sp^2)-C(sp^2)$-Bindung (87–120 kJ/mol, Tab. 5) wurden ermittelt. Diese Energiebeträge werden im Hinblick auf den Raumbedarf von *ortho*-Substituenten und die Stützeffekte durch *meta*-Substituenten diskutiert.

The ground state of *N,N*,2,6-tetrasubstituted benzamides is nonplanar and rotation about the C(aryl)–C(carbonyl) single bond has been studied by the coalescence of NMR signals[2–4]. If the barrier is sufficiently high, enantiomers (*M*) and (*P*) can be separated. This has been accomplished only for few aromatic carboxamides[4–6], the most elaborate ones being 3-carbamoylpyridines[6]. In order to compare interrelated benzamides with each other in a more systematic way, we chose the *N,N*-dimethyl-2,6-disubstituted molecules **1**–**13**, for which an enrichment of (*M*) and (*P*) around room temperature could be expected (cf. ref.[3,5,6]). We intended to investigate their chromatographic separation on triacetylcellulose[7] and, subsequently, their barriers to racemization. We included 2-*tert*-butyl-*N,N*-dimethylbenzamide (**14**) which is one of the few *ortho* monosubstituted amides, the enantiomers of which might be enriched.

Analytical HPLC Separation of Enantiomers

The enantiomers were characterized by their parameters (Table 1) on triacetylcellulose (Table 2). The amides can roughly be divided into three groups: **1**–**4** as well as **12** and **13** are weakly retained, i.e. their k values are low; they show medium enantioselectivities α_c and resolutions R_s. The (–)-enantiomers of the 2,6-dimethoxy compounds **8**–**11**, however, are more strongly retained ($k_- = 1.5-2.5$); their α_c and R_s results are correspondingly better, which means base-line separations. On the other hand, the amides **6** and **7** of the third group show k_+ values which are strongly enhanced with reference to the first group; this means excellent resolutions and exceptional enantioselectivities of 7.0 and 19.7, respectively. If the NH_2 groups in **6** and **7** are replaced by hydroxy substituents, two strongly overlapped peaks at $k = 0.4$ result in both cases[5]. This example shows that extreme substituent effects of unknown origin may simplify (or complicate) separations on this sorbent.

As a general rule, tertiary thioamides[9] are more retained[7] on triacetylcellulose than the corresponding amides. Therefore, the resolution is often higher for thioamides, i.e. their enantiomers are more easily separated.



	R^2	R^3	R^4	R^5	R^6
(±)-**1**	Me	Br	Me	H	Me
(±)-**2**	Me	NO_2	Me	H	Me
(±)-**3**	Me	NH_2	Me	H	Me
(±)-**4**	Me	Me	Me	H	Me
(±)-**5**	Cl	NO_2	H	H	Cl
(±)-**6**	Br	NH_2	Br	H	Br
(±)-**7**	I	NH_2	I	H	I
(±)-**8**	OMe	Cl	H	H	OMe
(±)-**9**	OMe	Br	H	H	OMe
(±)-**10**	OMe	I	H	H	OMe
(±)-**11**	OMe	NO_2	H	H	OMe
(±)-**12**	benzo		H	H	Me
(±)-**13**	benzo		benzo		Me
(±)-**14**	tBu	H	H	H	H

Enrichment of Enantiomers

Semipreparative liquid chromatography on triacetylcellulose gave enantiomers which were collected at ca. 5°C. Several injections of 30–40 mg of racemate yielded enriched enantiomers, depending on the resolution and on the rate

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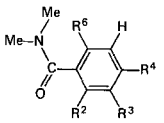
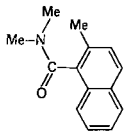
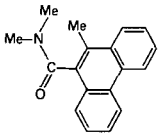
of racemization. Ethanol was removed at reduced pressure at 0–5 °C.

Table 1. Parameters used in Table 2

Parameter	Symbol	Definition
Capacity factor of solute i	k_i	
Retention volume of solute i	v_i	
Dead volume of a nonretained substance	v_o	
Enantioselectivity	α_c	k_2/k_1
Resolution	R_s	$2(v_2 - v_1)/(w_2 + w_1)$
Base-width of a peak	w	

Table 2. HPLC data (cf. Table 1) on triacetylcellulose (8–15 μm) at 22 °C. Eluent: EtOH:H_2O (96:4); flow rate: 2.0 ml/min



Comp. no.	$R^2=R^6$	R^3	R^4	k_+	k_-	α_c	R_s
4	Me	Me	Me	0.5	0.3	2.0	1.1
1	Me	Br	Me	0.4	0.7	1.8	1.1
3	Me	NH_2	Me	0.8	0.5	1.6	1.0
2	Me	NO_2	Me	0.8	0.5	1.6	1.1
5	Cl	NO_2	H	1.1		≈1	—
6	Br	NH_2	Br	6.1	0.9	7.0	4.2
7	I	NH_2	I	18.4	0.9	19.7	4.6[1]
8	OMe	Cl	H	0.4	1.7	4.0	3.1
9	OMe	Br	H	0.5	2.5	5.2	3.8
10	OMe	I	H	0.5	2.3	5.0	3.3
11	OMe	NO_2	H	0.8	1.5	1.8	1.7
12				0.8	0.5	1.5	1.0
13				0.7	0.5	1.4	0.6

Enantiomeric Purities and Specific Rotations of the Pure Enantiomers

Enantiomeric purities were determined using ^{1}H NMR in the presence of (+)-tris(heptafluorobutyryl-*d*-camphorato)europium(III), (+)-Eu(hfbc)$_3$, and/or by known liquid chromatographic methods[10,11] (Table 3).

Integration of baseline-separated peaks in chromatography is particularly useful for the determination of enantiomeric purity P_{int}. However, not all racemates gave good separations and it became necessary to decompose[7,11] partially overlapped peaks or to use the ratio of two slopes[10]. Decomposition can be done by hand, or by the computer program ZERLEG[11] if double detection by a photometer and a polarimeter after chromatography is performed. The areas of decomposed $A(v)$ or $\alpha(v)$ curves can then be calculated[11].

Table 3. Enantiomeric purities P (in %) as determined by ^{1}H NMR in the presence of (+)-Eu(hfbc)$_3$ (P_{nmr}), decomposition of overlapped peaks[11] (P_{dec}), ratio of two slopes[10] (P_{two}), and integration of the UV curve (P_{int}); x = [Eu(hfbc)$_3$]/[amide]

Comp. no.	x	P_{nmr}	P_{dec}	P_{two}	P_{int}
(−)-**1**	0.61	90 ± 2	–	–	88 ± 2
(+)-**2**	0.28	87 ± 2	–	–	82 ± 2
(−)-**3**	0.45	69 ± 4	69 ± 6	69 ± 6	–
(−)-**4**	0.50	88 ± 2	–	–	92 ± 2
(−)-**6**	0.32	98 ± 2	–	99 ± 2	99 ± 2
(+)-**7**	0.46	99 ± 2	–	–	–
(−)-**8**	0.28	7 ± 2	low barrier to rotation		
(−)-**9**	0.27	7 ± 2	low barrier to rotation		
(+)-**10**	0.32	8 ± 2	low barrier to rotation		
(+)-**11**	0.46	90 ± 2	–	–	–
(−)-**5**	0.42	42 ± 2	poor separation		
(+)-**12**	0.40	90 ± 2	–	–	92 ± 2

Table 4. Specific rotations $[\alpha_o]$ of pure enantiomers, in deg ml g^{-1} dm^{-1}. P_{lc} refers to either of the three methods, the results of which are given in Table 3. $[\alpha_o]$ for procedures using P_{nmr} and P_{lc} are calculated from $[\alpha_o] = [\alpha]/P$. The concentrations for the $[\alpha]$ measurements ranged from 1 to 8 g l^{-1}, depending on α and transmission of light. See text for determination of $[\alpha_o]$ without preparative enrichment

Comp. no.	λ[nm]	T[°C]	Solvent	Using P_{nmr}	Using P_{lc}	Without prep. enrichment
1	365	22	dioxane	22 ± 3	22 ± 3	–
2	436	22	dioxane	117 ± 11	125 ± 12	–
3	365	22	EtOH	146 ± 16	146 ± 14	–
4	365	22	dioxane	14 ± 3	13 ± 3	–
6	365	22	EtOH	106 ± 7	106 ± 7	–
7	365	22	EtOH	200 ± 15	–	–
8	365	21	EtOH		–	306 ± 19[a] 285 ± 18[b]
9	365	20	EtOH		–	291 ± 15[a]
10	365	20	EtOH			310 ± 16[a]
11	436	21	EtOH	119 ± 16	–	108 ± 8[b]
5	436	22	EtOH	57 ± 6	–	–
12	365	22	EtOH	71 ± 6	69 ± 6	–

[a] Slope (see text) at 0 °C is used. – [b] Slope (see text) at 20 °C is used.

Double detection is also necessary for the method using the ratio of two slopes[10], i.e. the slope for the enriched enantiomer, chromatographed on silica gel, and the slope for the racemate, chromatographed on triacetylcellulose. The error of both methods is essentially given by the errors of the slopes.

The enantiomeric purities of **8**–**11** were difficult to determine due to low barriers to rotation, such that the specific rotations of the pure enantiomers (Table 4) were determined without preparative enrichment. A modification of the known method[11,12] integrates the UV peaks of the chromatogram and, with knowledge of the amount of racemate injected and the slope, computes the specific rotation of the pure enantiomer.

All the methods agree well with each other (Tables 3 and 4). For most aromatic amides, ^{1}H NMR has a clear advantage over chromatographic procedures especially in the case of small specific rotations and low capacity factors, which create problems for methods requiring the slope[10]. Since the carbonyl groups complex well with (+)-Eu(hfbc)$_3$, splittings are usually found and a Eu(hfbc)$_3$-to-sub-

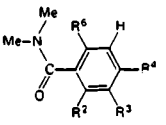
strate ratio for baseline splitting can be found. The temperature during the NMR measurement can be adjusted so that racemization is negligible.

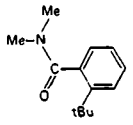
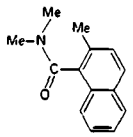
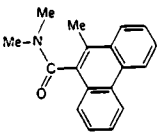
Thermal Racemization of Enantiomers

The enriched enantiomers were thermally racemized in order to determine the barriers to rotation about the C(carbonyl)–C(aryl) bond (Table 5). The entropies of activation for **9** and **12** were also determined, in order to check the reliability of comparing the barriers at a uniform temperature (Table 5). For compounds which are not analogous to **9** or **12**, an estimated value of -30 J mol^{-1} K^{-1}, with a large error, was used in Table 5.

Due to its low barrier to rotation, **14** was racemized without preparative enrichment[4]. Chromatography at 0°C was interrupted at maximum polarimeter readout, the enriched fraction trapped and investigated at constant temperature.

Table 5. $\Delta G^{\neq}$ Values determined at racemization temperatures T and converted to 61°C by means of the $\Delta S^{\neq}$ value indicated (cf. text). Solvents: Absol. dioxane, except for **14** (ethanol)



Comp. no.	$R^2=R^6$	R^3	R^4	$\Delta G^{\neq}$ (T) [kJ/mol]	T [°C]	$\Delta G^{\neq}$ (61°C) [kJ/mol]
14				86.9 ± 0.1	12.5	88.3 ± 1.1[a]
8	OMe	Cl	H	94.3 ± 0.1	31.0	95.4 ± 0.2[b]
9	OMe	Br	H	94.7 ± 0.1	30.5	95.8 ± 0.2[b]
10	OMe	I	H	95.0 ± 0.1	36.7	95.9 ± 0.2[b]
11	OMe	NO_2	H	96.6 ± 0.1	33.4	97.6 ± 0.2[b]
12				100.7 ± 0.1	50.1	100.9 ± 0.2[c]
2	Me	NO_2	Me	101.8 ± 0.1	55.9	102.0 ± 0.2[a]
3	Me	NH_2	Me	103.3 ± 0.8	54.8	103.5 ± 0.9[a]
4	Me	Me	Me	103.8 ± 0.1	60.9	103.8 ± 0.1
1	Me	Br	Me	104.6 ± 0.4	68.4	104.4 ± 0.6[a]
13				112.2 ± 0.2	71.5	112.0 ± 0.2[c]
5	Cl	NO_2	H	113.4 ± 0.1	75.8	112.9 ± 0.4[a]
6	Br	NH_2	Br	116.4 ± 0.4	84.9	115.7 ± 0.9[a]
7	I	NH_2	I	120.4 ± 0.1	100.0	119.2 ± 1.0[a]

[a] $\Delta S^{\neq} = -30 \pm 20$ J mol^{-1} K^{-1}. – [b] $\Delta S^{\neq} = -37 \pm 4$ J mol^{-1} K^{-1}. – [c] $\Delta S^{\neq} = -19 \pm 2$ J mol^{-1} K^{-1}.

Discussion of the Barriers to Enantiomerization

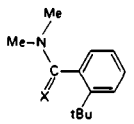
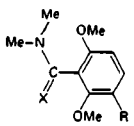
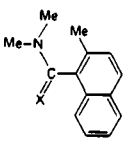
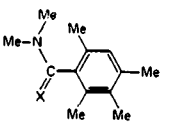
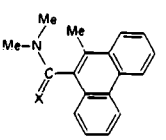
As expected, increasing size of *ortho* substituents increases the barrier to rotation (Table 5). Electronegative substituents, however, can significantly increase the barrier due to repulsion with the carbonyl oxygen, e.g. in **5**. Similar observations were made for corresponding thioamides[9].

The *tert*-butyl group in **14** was sufficient to raise the barrier to the limits of chromatographic separation. The barrier of about 87 kJ/mol in ethanol gives rise to overlapped peaks at room temperature due to racemization, but cooling the column gives a good chromatogram.

Buttressing groups (R^3) also increase the barrier, depending on their size, inductive and mesomeric effects. It is difficult to say, however, to which extent these different factors contribute. The buttressing effects can be empirically summarized as follows: I > Br > Cl, Me > OMe, NH_2. The effect of the nitro group varies, depending on the geometry with respect to the benzene plane. If the NO_2 substituent lies nearly in the plane, the effect in the amide **11** is greater than that of iodine in **10**; if it is perpendicular to the benzene plane[13,14], the effect in amide **2** is less than that of the amino group in **3**.

7 (120.4 kJ/mol, 100.0°C, absol. dioxane, Table 5) can be compared with the amide bearing an additional carboxyl group in the 5-position (3-amino-5-carboxy-2,4,6-triiodo-*N*,*N*-dimethylbenzamide[5] (≈ 131 kJ/mol, 117°C, 1-butanol). Although the unequal solvents prevent a detailed comparison, the buttressing effect seems to operate in this case, too. This is also true for *N*,*N*,2,6-tetramethyl-3-*aza*benzamide (3-carbamoyl-*N*,*N*,2,4-tetramethylpyridine[6], 90 kJ/mol, 27°C, *n*-hexane) compared with *N*,*N*,2,4,6-pentamethyl-*3-nitro*benzamide (**2**, 101.8 kJ/mol, 55.9°C, absol. dioxane, Table 5). As expected, the buttressing effect by the lone pair

Table 6. $\Delta G^{\neq}$ Values for aromatic amides and thioamides[11]. Diglyme, Ph_2O, and absol. dioxane as solvents give approximately the same $\Delta G^{\neq}$ values (see text)

	R	X	No.	Solvent	T [°C]	$\Delta G^{\neq}$ [kJ/mol]	$\Delta\Delta G^{\neq}$ [kJ/mol]
	–	O	**14**	EtOH	12.5	86.9 ± 0.1	39.4
	–	S	**14s**	diglyme	89.9	126.3 ± 0.2	
	Cl	O	**8**	dioxane	31.0	94.3 ± 0.1	30.4
	Cl	S	**8s**	diglyme	89.1	124.7 ± 0.1	
	Br	O	**9**	dioxane	30.5	94.7 ± 0.1	30.2
	Br	S	**9s**	diglyme	89.9	124.9 ± 0.1	
	–	O	**12**	dioxane	54.9	100.3 ± 0.2	38.4
	–	S	**12s**	diglyme	159.1	138.7 ± 0.2	
	–	O	**4**	dioxane	60.9	103.8 ± 0.1	33.7
	–	S	**4s**	diglyme	158.9	137.5 ± 0.1	
	–	O	**13**	Ph_2O	71.5	112.2 ± 0.2	33.3
	–	S	**13s**	Ph_2O	160.1	145.5 ± 0.1	

in the 3-azabenzamide (if any) is smaller than the one by the NO_2 group in the 3-nitrobenzamide **2**.

Substitution of oxygen by sulfur[11] increases the barrier to rotation by 30–40 kJ/mol (Table 6). The bulky sulfur atom may hinder the pseudo-planar transition state, where only the *N*-methyl groups move out of the common plane due to some rotation about the $N(sp^2)-C(sp^2)$ bond. Approximately the same $\Delta G^{\neq}$ values have been found[8,11] in different solvents used for the racemizations – diglyme, diphenyl ether, and absol. dioxane.

The barriers to rotation about the $C(sp^2)-C(sp^2)$ bond (Table 5) are similar in magnitude to the ones for the corresponding $N(sp^2)-C(sp^2)$ motion[15], although results which can be strictly compared are not yet available. This situation rises the question whether the above two rotations represent consecutive or, in some cases, synchronous processes[16]. Work is in progress[17] to contribute to the solution of this problem by using the method of separation and the results of enantiomerizations described in the present paper.

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Experimental

Melting points: Büchi SMP 20; not corrected for temperatures above 150°C. – IR spectra: Beckman AccuLab 1. – High-resolution MS: Varian MAT 311A or Varian CH5, both at 70 eV and a source temperature of 150°C. – ^{1}H-NMR spectra: Varian T-60 (CW mode, 60 MHz, accuracy ± 0.04 ppm), Bruker WH-90 (PFT mode, 90 MHz, accuracy ± 0.02 ppm). – UV spectra: Beckman Model 24. – Specific rotations: Perkin Elmer 241.

Lanthanoide-Induced Shifts and Splittings: (+)-Tris(3-heptafluorobutyryl-d-camphorato)europium(III), 99% pure, was obtained from Aldrich Chemical Company, Inc. $[\alpha]_{589}^{22}$ = 170 deg ml g^{-1} dm^{-1} in CCl_4 (ref.[18] 169 deg ml g^{-1} dm^{-1}). This reagent was added in gradual proportions to 0.2 M solutions of the (±)-amides in $CDCl_3$ and the corresponding spectra were recorded. It was also added to enriched enantiomers for the determination of enantiomeric purity. The ratio of reagent to amide was varied in order to obtain baseline splittings.

Analytical Low-Pressure Liquid Chromatography: The sorbent used for analytical as well as semipreparative columns was swollen microcrystalline triacetylcellulose prepared as described[19], ground and presieved. After fractionation (Zickzacksichter A100 MZR Alpine AG, Augsburg) particle sizes 20–30 μm and 30–60 μm were slurry-packed in glass columns (2.5 × 30 cm, Serva GmbH, Heidelberg; or 2.5 cm diameter with variable length[11] up to 20 cm) at 7–8 bar as described[19]. – Chromatography was carried out at 1.5 (0–25°C) to ≈5 bar (>40°C) using a membrane pump ProMinent Electronic B2505 or SI (Chemie und Filter GmbH, Heidelberg) with flow rates between 1.7 and 5.0 ml/min and temperatures between 0 and 60°C. The usual chromatographic conditions were 1.5–2.0 bar, 3.7–4.0 ml/min, and 20–26°C. The eluent was EtOH:H_2O (96:4). – Detections were carried out using a photometer (Uvicord S, LKB) with a double-cell[10] and a polarimeter (Perkin-Elmer 241) with a glass cuvette (100 × 3 mm). 253-, 278-, and 365-nm filters for the photometer were used. The polarimeter wavelengths were 365 and 436 nm. – Chromatographic data were recorded and stored by an on-line ALTOS Microcomputer, equipped with a terminal (Visual 200), a printer (C. Itoh Electronics, Inc.), and a plotter (Digi-Plot, Watanabe WX 4671). The computer software was prepared by Eiglsperger[11].

Semipreparative Low-Pressure Liquid Chromatography: Separation of enantiomers was achieved by several injections of 30–40 mg of racemate, collecting at parts of the chromatogram where a pure or enriched enantiomer is eluted. In cases of overlap, the middle fractions were collected and reinjected. 150 mg of racemate yielded about 50–60 mg of each enantiomer. In cases of partial racemization on the column, the yield of enriched enantiomer was lower, depending on the barrier to rotation. The enantiomers of **4** and **9** racemize upon crystallization. The enantiomers of **6** were accompanied by some impurities, as detected by NMR and mass spectrometry.

Analytical HPLC: The columns were prepared and used like Columns B and C in ref.[20]. The packing pressure was 150 bar. A Hewlett-Packard chromatograph (Model 1084B) with UV detection at 278 nm was used.

Thermal Racemizations: These were performed in absol. dioxane (Uvasol, E. Merck, dried, and distilled over sodium) or in EtOH:H_2O (96:4), using the polarimeter (Perkin Elmer 241) over at least two half-lives. The barriers to rotation (Tables 5 and 7) were computed using the program[21] KIN 32.

Table 7. Results of racemization of **9** and **12** in absol. dioxane. The errors of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were determined by drawing rectangles in the Eyring plot indicating maximal errors and considering the deviations from the slope and intercept

Comp. no.	T [°C]	k [s^{-1}]	$\Delta G^{\neq}$ (T) [kJ/mol]	$\Delta H^{\neq}$ [kJ/mol]	$\Delta S^{\neq}$ [J mol^{-1} K^{-1}]
9	50.3	$2.5 \cdot 10^{-3}$	95.4 ± 0.1	84 ± 8	−37 ± 4
	40.2	$8.3 \cdot 10^{-4}$	95.3 ± 0.1		
	30.5	$3.1 \cdot 10^{-4}$	94.7 ± 0.1		
	20.0	$9.1 \cdot 10^{-5}$	94.4 ± 0.1		
12	64.1	$1.4 \cdot 10^{-3}$	101.3 ± 0.1	95 ± 5	−19 ± 2
	50.1	$3.4 \cdot 10^{-4}$	100.7 ± 0.1		
	40.2	$1.1 \cdot 10^{-4}$	100.7 ± 0.1		
	27.7	$2.1 \cdot 10^{-5}$	100.5 ± 0.1		
	25.3	$1.6 \cdot 10^{-5}$	100.4 ± 0.1		

3-Bromo-2,4,6-trimethylbenzoic Acid (3-Bromomesitoic Acid)[22,23]: Bromine (13.5 g, 84.4 mmol) was added dropwise, with stirring and reflux, to 2,4,6-trimethylbenzoic acid (13.0 g, 79.2 mmol), iron powder (1.0 g), and CCl_4 (25 ml). After complete addition, the reaction mixture was stirred for 30 min, cooled, and filtered. The crude product was washed with 40% aq. HCl, dissolved in excess 5% aq. NaOH, and filtered. The filtrate was neutralized to precipitate the acid. Recrystallization from 75% ethanol gave fine colorless needles, m.p. 162.0–162.5°C (ref.[23] 163.5°C), yield 54%. – ^{1}H NMR ($CDCl_3$): δ = 2.32 (s; 3H, CH_3), 2.41 (s; 3H, CH_3), 2.47 (s; 3H, CH_3), 6.97 (s; 1H, 5-H).

2,4,6-Trimethyl-3-nitrobenzoic Acid (3-Nitromesitoic Acid)[23]: Recrystallization from 50% ethanol gave yellowish needles, m.p. 183.5–184.0°C (ref.[23] 182°C), yield 84%. – ^{1}H NMR ($CDCl_3$): δ = 2.30 (s; 3H, CH_3), 2.35 (s; 3H, CH_3), 2.42 (s; 3H, CH_3), 7.01 (s; 1H, 5-H), 8.90 (broad s; OH).

3-Amino-2,4,6-trimethylbenzoic Acid (3-Aminomesitoic Acid)[23]: 2,4,6-Trimethyl-3-nitrobenzoic acid (1.0 g, 4.2 mmol) was dissolved in 50 ml of ethanol. Pd (100 mg, or 1.0 g of 10% Pd on active

carbon) was added, and H_2 was bubbled through the mixture until uptake ceased. The catalyst was filtered off and the solvent evaporated. The acid was converted into its chloride without further purification; m.p. >180°C (ref.[23] 209–210°C). – ^{1}H NMR ([D$_8$]THF): δ = 2.07 (s; 6H, two CH_3 groups), 2.14 (s; 3H, CH_3), 6.64 (s; 1H, 5-H).

2,3,4,6-Tetramethylbenzoic Acid[23]: The procedure of Sokol[24] for analogous aryl compounds was used. Oxalyl chloride (13.9 g, 0.11 mol) was added dropwise to dry $AlCl_3$ (14.6 g, 0.54 mol) in dry CS_2 (70 ml). Isodurene (13.5 g, 0.10 mol) in dry CS_2 (20 ml) was added dropwise with stirring, refluxed for an hour, poured into ground ice (200 g) with 30 ml of 12 N HCl, and extracted with CCl_4. The organic phase was extracted with cold 10% aq. NaOH. The aqueous phase was poured into 6 N HCl, filtered, and washed with H_2O. Recrystallization from low-boiling petroleum ether, m.p. 163–164°C (ref.[23] 164–165°C), yield 45%. – ^{1}H NMR ($CDCl_3$): δ = 2.18 (s; 3H, CH_3), 2.28 (s; 3H, CH_3), 2.35 (s; 6H, two CH_3 groups), 6.84 (s; 1H, 5-H).

2,6-Dichloro-3-nitrobenzoic Acid: 2,6-Dichlorobenzoic acid (2.0 g, 10 mmol) was dissolved, with heating, in conc. H_2SO_4 (75 ml). Conc. HNO_3 (0.78 ml) was slowly added, and the solution was heated and stirred for one hour. The solution was poured into ground ice (300 g) and kept cool until crystallization. The product was filtered while cold since it was partially soluble in water; long colorless plates, m.p. 143–144°C, yield 65%. – ^{1}H NMR ([D$_6$]DMSO): δ = 4.80 (broad s; OH), 7.68, 7.36 (AB system; 2H, 4-H, 5-H, J = 9 Hz).

3-Amino-2,4,6-tribromobenzoic Acid[25]: The product was used in the next stages without recrystallization; white powder, m.p. 174–175°C (ref.[25] 173°C). – ^{1}H NMR ([D$_6$]acetone): δ = 5 (broad s; NH_2), 7.62 (s; 1H, 5-H).

3-Amino-2,4,6-triiodobenzoic Acid[26]: The crude product was dissolved in hot water, heated and stirred with active carbon, filtered, and cooled. The suggestion to first make the Na-salt[26] was omitted; colorless needles, m.p. 199.0–199.5°C (ref.[26] 196.5–197.5°C), yield 60%. – ^{1}H NMR ([D$_6$]DMSO): δ = 5.38 (broad s; NH_2), 7.95, 8.13 (2s; 5-H and OH).

Table 8. Melting points, yields, and elemental analyses of racemates. Systematic names are *N,N*,2-trimethyl-1-naphthalenecarboxamide (**12**) and *N,N*,10-trimethyl-9-phenanthrenecarboxamide (**13**), all others being derived from *N,N*-dimethylbenzamide

Comp. no.	M.p. [°C]	% Yield	Elemental Analysis
(±)-**1**	34.0–34.5 colorless	80	Calcd. C 53.35 H 5.97 Br 29.58 N 5.18 Found C 53.03 H 5.94 Br 29.59 N 5.29
(±)-**2**	80.0–80.4 light yellow	55	Calcd. C 61.00 H 6.77 N 11.85 Found C 60.96 H 6.47 N 12.04
(±)-**3**	89.5–91.0 fawn	40	Calcd. C 69.80 H 8.80 N 13.58 Found C 69.48 H 9.01 N 13.70
(±)-**4**	48.0–48.5 colorless	80	Calcd. C 76.06 H 9.33 N 6.82 Found C 75.89 H 9.03 N 6.57
(±)-**5**[a]	65–66 yellow	12	Calcd. C 41.09 H 3.07 N 10.65 Found C 41.27 H 3.33 N 10.59
(±)-**6**	120–121 colorless	40	Calcd. C 27.00 H 2.27 Br 59.89 N 7.00 Found C 26.74 H 2.35 Br 59.65 N 7.07
(±)-**7**[b]	155, decom. yellow	40	Calcd. C 19.95 H 1.67 N 5.17 Found C 19.67 H 1.61 N 4.83
(±)-**8**	85.0–86.5 colorless	71	Calcd. C 54.24 H 5.79 N 5.75 Found C 54.28 H 5.86 N 5.80
(±)-**9**	74.0–74.5 colorless	20	Calcd. C 45.85 H 4.90 Br 27.73 N 4.86 Found C 45.74 H 4.88 Br 27.71 N 4.86
(±)-**10**	120–121 colorless	20	Calcd. C 39.66 H 3.63 N 4.20 Found C 39.83 H 3.66 N 4.14
(±)-**11**	109–110 light-yellow	41	Calcd. C 51.97 H 5.55 N 11.02 Found C 51.84 H 5.67 N 10.95
(±)-**12**[11]	55 colorless	70	Calcd. C 78.27 H 6.58 N 7.03 Found C 78.00 H 6.61 N 7.00
(±)-**13**[11]	147–148 colorless	79	Calcd. C 82.10 H 6.58 N 5.32 Found C 82.14 H 6.49 N 5.26
(±)-**14**[11]	48–49.5 colorless	68	Calcd. C 76.06 H 9.32 N 6.82 Found C 75.92 H 8.97 N 6.80

[a] MS, molecular ion: Calcd. 261.9912, Found 261.9986. – [b] MS, molecular ion: Calcd. 541.7844, Found 541.7843.

Table 9. UV ($CHCl_3$) and ^{1}H-NMR ($CDCl_3$) data of racemates

Comp. no.	λ_{max} [nm] (lg ε)	δ Values
(±)-**1**	245 (3.17), 274 (2.56), 280 (2.42)	2.13 (s; 3H, CH_3), 2.29 (s; 3H, CH_3), 2.38 (s; 3H, CH_3), 2.76 (s; 3H, NCH_3^E), 3.11 (s; 3H, NCH_3^Z), 6.87 (s; 1H, 5-H)
(±)-**2**	243 (3.42), 270 (3.21), 348 (2.70)	2.17 (s; 3H, CH_3), 2.24 (s; 3H, CH_3), 2.27 (s; 3H, CH_3), 2.81 (s; 3H, NCH_3^E), 3.13 (s; 3H, NCH_3^Z), 7.00 (s; 1H, 5-H)
(±)-**3**	247 (3.53), 295 (3.62)	2.04 (s; 3H, CH_3), 2.11 (s; 3H, CH_3), 2.14 (s; 3H, CH_3), 2.78 (s; 3H, NCH_3^E), 3.14 (s; 3H, NCH_3^Z), 6.80 (s; 1H, 5-H)
(±)-**4**	245 (2.83), 271 (2.68), 279 (2.01)	2.13 (s; 9H, 3 CH_3 groups), 2.27 (s; 3H, CH_3), 2.78 (s; 3H, NCH_3^E), 3.13 (s; 3H, NCH_3^Z), 6.79 (s; 1H, 5-H)
(±)-**5**	264 (3.73), 355 (sh)	2.88 (s; 3H, NCH_3^E), 3.18 (s; 3H, NCH_3^Z), 7.79, 7.46 (AB system; 2H, J = 9 Hz, 4-, 5-H)
(±)-**6**	249 (3.52), 316 (3.06)	2.86 (s; 3H, NCH_3^E), 3.13 (s; 3H, NCH_3^Z), 4.68 (s; 2H, NH_2), 7.51 (s; 1H, 5-H)
(±)-**7**	262 (4.14), 318 (3.65)	3.06 (s; 3H, NCH_3^E), 3.33 (s; 3H, NCH_3^Z), 5.03 (broad s; NH_2), 8.19 (s; 1H, 5-H)
(±)-**8**	288 (3.33)	2.80 (s; 3H, NCH_3^E), 3.12 (s; 3H, NCH_3^Z), 3.79 (s; 3H, OCH_3), 3.88 (s; 3H, OCH_3), 7.30, 6.63 (AB system; 2H, J = 9 Hz, 4-, 5-H)
(±)-**9**	289 (3.32)	2.81 (s; 3H, NCH_3^E), 3.13 (s; 3H, NCH_3^Z), 3.79 (s; 3H, OCH_3), 7.43, 6.58 (AB system; 2H, J = 9 Hz, 4-, 5-H)
(±)-**10**	285 (3.36)	2.81 (s; 3H, NCH_3^E), 3.13 (s; 3H, NCH_3^Z), 3.80 (s; 3H, OCH_3), 3.85 (s; 3H, OCH_3), 7.67, 6.51 (AB system; 2H, J = 9 Hz, 4-, 5-H)
(±)-**11**	300 (3.82)	2.83 (s; 3H, NCH_3^E), 3.16 (s; 3H, NCH_3^Z), 3.92 (s; 3H, OCH_3), 3.95 (s; 3H, OCH_3), 8.00, 6.75 (AB system; 2H, J = 9 Hz, 4-, 5-H)
(±)-**12**	275 (3.89), 283 (3.92), 320 (2.80)	2.41 (s; 3H, 2-CH_3), 2.72 (s; 3H, NCH_3^E), 3.26 (s; 3H, NCH_3^Z), 7.27–7.86 (m; 6H, aromatic H)
(±)-**13**	250 (4.67), 256 (4.76), 270 (4.04), 278 (4.11), 289 (4.01), 318 (2.46), 325 (2.38), 333 (2.44), 340 (2.33), 349 (2.29)	2.64 (s; 3H, 10-CH_3), 2.77 (s; 3H, NCH_3^E), 3.29 (s; 3H, NCH_3^Z), 7.65 (m; 2-, 3-, 6-, 7-H), 8.10 (m; 1-, 8-H), 8.70 (m; 4-, 5-H)
(±)-**14**	260 (2.51), 265 (2.49)	1.38 (s; 9H, C–CH_3), 2.77 (s; 3H, NCH_3^E), 3.07 (s; 3H, NCH_3^Z), 7.57–6.86 (m; 4H, 3-, 4-, 5- and 6-H)

3-Chloro-2,6-dimethoxybenzoic Acid: 2,6-Dimethoxybenzoic acid (4.55 g, 25 mmol) was dissolved in dry ether (75 ml). Sulfuryl chloride (2.2 ml) was added and the solution refluxed for 30 min. Ether and excess sulfuryl chloride were distilled. The acid was extracted with 3% $NaHCO_3$ solution, neutralized with dilute HCl, and allowed to stand until crystallization; colorless plates, m.p. 135–136°C (ref.[27] 133°C), yield 40%. – ^1H NMR ($CDCl_3$): δ = 3.86 (s; 3H, OCH_3), 3.95 (s; 3H, OCH_3), 6.35 (broad s; OH), 7.33, 6.65 (AB system, 2H; 4-H, 5-H, J = 9 Hz).

3-Bromo-2,6-dimethoxybenzoic Acid: Bromine (1 ml, 19 mmol) in glacial acetic acid (30 ml) was added dropwise to 2,6-dimethoxybenzoic acid (3.1 g, 17 mmol) in glacial acetic acid. The yellow-orange suspension was stirred for 90 min, poured into ground ice (300 g), and allowed to stand until the product crystallized; colorless plates, m.p. 145.5–146.0°C (ref.[27] 146°C), yield 97%. – ^1H NMR ($CDCl_3$): δ = 3.85 (s; 3H, OCH_3), 3.93 (s; 3H, OCH_3), 5.60 (broad s; OH), 7.48, 6.61 (AB system; 2H, 4-H, 5-H, J = 9 Hz).

3-Iodo-2,6-dimethoxybenzoic Acid: 2,6-Dimethoxybenzoic acid (4.5 g, 25 mmol) in H_2O (100 ml) and conc. HCl (2.5 ml) was halogenated with iodine monochloride (5 g, 30 mmol) in 5 ml of conc. HCl at 80°C. The mixture was stirred for 3 h and poured into ground ice (300 g); colorless needles, m.p. 160–162°C (ref.[27] 162°C), yield 78%. – ^1H NMR ($CDCl_3$): δ = 3.89 (s; 3H, OCH_3), 3.95 (s; 3H, OCH_3), 7.75, 6.56 (AB system; 2H, 4-H, 5-H, J = 9 Hz).

2,6-Dimethoxy-3-nitrobenzoic Acid[27]: Yellowish needles, m.p. 129–131°C (ref.[27] 131.5–132.0°C), yield 41%. – ^1H NMR ($CDCl_3$): δ = 3.96 (s; 3H, OCH_3), 4.00 (s; 3H, OCH_3), 7.50 (broad s; OH), 8.05, 6.74 (AB system; 2H, 4-H, 5-H, J = 9 Hz).

Table 10. Characteristics of enriched enantiomers. For capacity factors and specific rotations of pure enantiomers see Tables 2 and 4, for enantiomeric purities Table 3

Comp. no.		M.p. [°C]	Description
1	(+)	–	colorless oil
	(–)	–	
2	(+)	88–90	yellow powder
	(–)	85–90	
3	(+)	–	reddish oil
	(–)	–	
4	(+)	–	colorless oil that
	(–)	–	racemizes on crystallization
5	(+)	–	yellow oil
	(–)	–	
6	(+)	112–118	fawn-colored solid
	(–)	114–119	
7	(+)	158, dec.	cream-colored powder
	(–)	156, dec.	
8	(+)	87–90	white powder
	(–)	91–92	
9	(+)	–	colorless oil that
	(–)	–	racemizes on crystallization
10	(+)	116–120	white powder
	(–)	114–118	
11	(+)	109–110	white powder
	(–)	114–118	
12	(+)	81–85	white powder
	(–)	86–89	
13	(+)	94–96	white powder
	(–)	90–94	

2-Methyl-1-naphthoic Acid[11,28]: M.p. 98–114°C (ref.[28] 126–127°C), yield 36%. – ^1H NMR ($CDCl_3$): δ = 3.00 (s; 3H, 2-CH_3), 7.1–8.2 (m; 6H, aromatic H), 12.10 (s; COOH).

10-Methylphenanthrene-9-carboxylic Acid[11,29]: M.p. 206.0 bis 207.5°C (ref.[29] 207.5–208.5°C), yield 66%. – ^1H NMR ([D_6]-acetone): δ = 2.74 (s; 3H, 10-CH_3), 7.50–8.99 (m; 8H, aromatic H).

2-tert-Butylbenzoic Acid[11,30]: M.p. 67–68°C (ref.[30] 68.5°C), yield 8%. – ^1H NMR ($CDCl_3$): δ = 1.47 (s; 9H, C–CH_3), 7.0–7.6 (m; 4H, aromatic H), 11.56 (s; COOH).

General Procedure for N,N-Dimethylcarboxamides: The crude acid chloride, prepared by the standard procedure, was dissolved in absol. ether or tetrahydrofuran, and gaseous *N,N*-dimethylamine was bubbled through the solution until no more salt was formed. The mixture was filtered, the solvent rotated off, and the product dissolved in chloroform. The solution was extracted with water, the organic phase dried with anhydrous sodium or magnesium sulfate, and the solvent evaporated. The crude amide was recrystallized and characterized by its m.p., elemental analysis (Table 8), UV and ^1H-NMR data (Table 9). The enriched enantiomers were also characterized (Table 10).

CAS Registry Numbers

(±)-**1**: 106567-13-9 / (+)-**1**: 106567-42-4 / (–)-**1**: 106567-24-2 / (±)-**2**: 106587-52-4 / (+)-**2**: 106567-25-3 / (–)-**2**: 106567-43-5 / (±)-**3**: 106567-14-0 / (+)-**3**: 106567-44-6 / (–)-**3**: 106567-26-4 / (±)-**4**: 106567-15-1 / (+)-**4**: 106567-45-7 / (–)-**4**: 106567-27-7 / (±)-**4s**: 104124-97-2 / (±)-**5**: 106587-96-6 / (+)-**5**: 106567-46-8 / (–)-**5**: 106567-33-3 / (±)-**6**: 106567-16-2 / (+)-**6**: 106567-47-9 / (–)-**6**: 106567-28-6 / (±)-**7**: 104124-96-1 / (+)-**7**: 104124-95-0 / (–)-**7**: 104124-94-9 / (±)-**8**: 106567-17-3 / (+)-**8**: 106567-48-0 / (–)-**8**: 106567-29-7 / (±)-**8s**: 106567-35-5 / (±)-**9**: 106567-18-4 / (+)-**9**: 106567-49-1 / (–)-**9**: 106567-30-0 / (±)-**9s**: 106567-36-6 / (±)-**10**: 106567-19-5 / (+)-**10**: 106567-31-1 / (–)-**10**: 106567-50-4 / (±)-**11**: 106567-20-8 / (+)-**11**: 106567-32-2 / (–)-**11**: 106567-51-5 / (±)-**12**: 106567-21-9 / (+)-**12**: 106567-34-4 / (–)-**12**: 106567-52-6 / (±)-**12s**: 106587-53-5 / (±)-**13**: 106567-22-0 / (+)-**13**: 106567-38-8 / (–)-**13**: 106567-39-9 / (±)-**13s**: 106567-37-7 / (±)-**14**: 106567-23-1 / (±)-**14s**: 106624-49-1 / 3-bromomesitoic acid: 5333-13-1 / 2,4,6-trimethylbenzoic acid: 480-63-7 / 3-aminomesitoic acid: 106567-40-2 / 2,4,6-trimethyl-3-nitrobenzoic acid: 106567-41-3 / isodurene: 527-53-7 / 2,3,4,6-tetramethylbenzoic acid: 2408-38-0 / 2,6-dichloro-3-nitrobenzoic acid: 55775-97-8 / 2,6-dichlorobenzoic acid: 50-30-6 / 3-chloro-2,6-dimethoxybenzoic acid: 36335-47-4 / 2,6-dimethoxybenzoic acid: 1466-76-8 / 3-bromo-2,6-dimethoxybenzoic acid: 73219-89-3 / 3-iodo-2,6-dimethoxybenzoic acid: 90347-70-9 / 3-amino-2,4,6-tribromobenzoic acid: 6628-84-8 / 3-amino-2,4,6-triiodobenzoic acid: 3119-15-1 / 2,6-dimethoxy-3-nitrobenzoic acid: 55776-17-5 / 2-methyl-1-naphthoic acid: 1575-96-8 / 10-methylphenanthrene-9-carboxylic acid: 65698-59-1 / 2-*tert*-butylbenzoic acid: 1077-58-3

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