Supplementary material

Physical Property Differences Between Enantiopure and Racemic Methylephedrine Salts: Construction and Structural Analysis of a Systematic Series of Crystal Structures.

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CONTENTS

Supplementary Table S1: (Table 4 in main text). Graph-set analysis for chemically identical pairs of benzoate derivatives (a-anion, c-cation, w-water)

compound	hydrogen bond		graph-set		network growth	compound	hydrogen bond		graph-set		network growth
A1	a	$OH_c\cdots COO^-$	>a<b	$C_2^2(9)$	*a*	**A2**	a	$OH_c\cdots COO^-$	>a<b	$C_2^2(9)$	*a*
	b	$NH\cdots COO^-$					b	$NH\cdots COO^-$			
B1	a	$OH_c\cdots COO^-$	>b<c	$D_2^1(2)$	*a*	**B2**	a	$OH_c\cdots COO^-$	>b<c	$D_2^1(2)$	*b*
	b	$NH\cdots COO^-$	>a<c	$D_2^2(5)$			b	$NH\cdots COO^-$	>a<c	$D_2^2(5)$	
	c	$OH_w\cdots COO^-$	>a<d	$D_2^2(8)$			c	$OH_w\cdots COO^-$	>a<d	$D_2^2(8)$	
	d	$OH_w\cdots NO_2$	>b<d	$D_2^2(8)$			d	$OH_w\cdots NO_2$	>b<d	$D_2^2(8)$	
			>a<b	$C_2^2(9)$					>a<b	$C_2^2(9)$	
			>c<d	$C_2^2(9)$					>c<d	$C_2^2(9)$	
C1	a	$OH_c\cdots COO^-$	>a<b	$C_2^2(9)$	*a*	**C2**	a	$OH_c\cdots COO^-$	>a<b	$C_2^2(9)$	*b*
	b	$NH\cdots COO^-$					b	$NH\cdots COO^-$			
D1	a	$OH_c\cdots COO^-$	>c<d	$C_2^2(9)$	*a*	**D2**	a	$OH_c\cdots COO^-$	>a<b	$C_2^2(9)$	*a*
	b	$NH\cdots COO^-$	>a<b	$R_2^2(9)$			b	$NH\cdots COO^-$			
	c	$OH_c\cdots COO^-$									
	d	$NH\cdots COO^-$									
E1	a	$OH_c\cdots COO^-$	>a<b	$C_2^2(9)$	*b*	**E2**	a	$OH_c\cdots COO^-$	>a<b	$C_2^2(9)$	*b*
	b	$NH\cdots COO^-$					b	$NH\cdots COO^-$			

Supplementary Table S2: Graph-set analysis for five remaining pairs of benzoate derivatives (a-anion, c-cation, w-water)

compound	hydrogen bond		graph-set		network growth	compound	hydrogen bond		graph-set		network growth
N1	a	$OH_c\cdots COO^-$	>a<c	$D_2^1(3)$	*a b*	**N2**	a	$OH_c\cdots COO^-$	>a<b	$C_2^2(9)$	*b*
	b	$NH\cdots O_w$	>b>c	$D_2^2(4)$			b	$NH\cdots COO^-$			
	c	$OH_w\cdots COO^-$	>b>d	$D_2^2(4)$							
	d	$OH_w\cdots COO^-$	>a<d	$D_2^2(5)$							
			>c<d	$C_2^2(6)$							
			<a>b	$D_2^2(8)$							
O1	a	$OH_c\cdots COO^-$	>a<d	$D_2^1(3)$	*b*	**O2**	a	$OH_c\cdots COO^-$	>a<b	$C_2^2(9)$	*b*
	b	$NH\cdots COO^-$	>b<c	$D_2^1(3)$			b	$NH\cdots COO^-$			
	c	$OH_w\cdots COO^-$	>a<c	$D_2^2(5)$							
	d	$OH_w\cdots COO^-$	>b<d	$D_2^2(5)$							
			>c<d	$C_2^2(6)$							
			>a<b	$C_2^2(9)$							
R1	a	$OH_c\cdots COO^-$	>b<f	$D_2^1(3)$	*a b c*	**R2**	Crystallises as a conglomerate, same parameters as (1R,2S)(-)-Methylephedrinium 4-hydroxybenzoate				
	b	$NH\cdots COO^-$	>c<e	$D_2^1(3)$							
	c	$OH_c\cdots COO^-$	>a<f	$D_2^2(5)$							
	d	$NH\cdots COO^-$	>d<e	$D_2^2(5)$							
	e	$OH_a\cdots COO^-$	>a<b	$C_2^2(9)$							
	f	$OH_a\cdots COO^-$	>c<d	$C_2^2(9)$							
			>a>e	$D_2^2(10)$							
			>b>e	$D_2^2(10)$							
			>c>f	$D_2^2(10)$							
			>d>f	$D_2^2(10)$							
			>e>f	$C_2^2(16)$							
S1	a	$OH_c\cdots COO^-$	>b<c	$R_1^2(4)$	*b*	**S2**	Crystallises as a conglomerate, same parameters as, (1R,2S)(-)-Methylephedrinium 4-chlorobenzoate				
	b	$NH\cdots COO^-$	>a<b	$C_2^2(7)$							
	c	$NH\cdots COO^-$	>a<c	$C_2^2(9)$	*b*						
T1	a	$OH_c\cdots COO^-$	>a<b	$C_2^2(9)$		**T2**	Crystallises as a conglomerate, same parameters as, (1R,2S)(-)-Methylephedrinium ρ-toluate				
	b	$NH\cdots COO^-$									

Supplementary Table S3: Graph-set analysis of sulfonate methylephedrinium salts

compound	hydrogen bond		graph-set		network growth	compound	hydrogen bond		graph-set		network growth
F1	a	$OH_c\cdots SO_3$	>a<b	$C_2^2(9)$	*a*	**F2**	a	$OH_c\cdots SO_3$	>a<b	$C_2^2(9)$	*c*
	b	$NH\cdots SO_3$					b	$NH\cdots SO_3$			
G1	a	$OH_c\cdots SO_3$	>a<c	$D_2^2(8)$	*a c*	**G2**	a	$OH_c\cdots SO_3$	>a<a	$D_2^2(8)$	*c*
	b	$NH\cdots SO_3$	>a<d	$D_2^2(8)$			b	$NH\cdots SO_3$	>b<b	$D_2^2(8)$	
	c	$OH_c\cdots SO_3$	>b<c	$D_2^2(8)$					>a<b	$C_2^2(9)$	
	d	$NH\cdots SO_3$	>b<d	$D_2^2(8)$					>a<a>b<b	$C_4^4(24)$	
			>a<b	$C_2^2(9)$					>a<b>a<b	$R_4^4(24)$	
			>c<d	$C_2^2(9)$							
H1	a	$OH_c\cdots SO_3$	>a<d	$D_2^2(5)$	*b*	**H2**	a	$OH_c\cdots SO_3$	>a<d	$D_2^2(5)$	$\perp$ *b*
	b	$NH\cdots SO_3$	>b<e	$D_2^2(5)$			b	$NH\cdots SO_3$	>b<c	$D_2^2(5)$	
	c	$OH_c\cdots SO_3$	>c<f	$D_2^2(5)$			c	$OH_c\cdots SO_3$	<a>b	$D_2^2(8)$	
	d	$NH\cdots SO_3$	<a>b	$D_2^2(8)$			d	$NH\cdots SO_3$	<c>d	$D_2^2(8)$	
	e	$OH_c\cdots SO_3$	<c>d	$D_2^2(8)$							
	f	$NH\cdots SO_3$	<e>f	$D_2^2(8)$							
I1	a	$OH_a\cdots O_w$	>c<d	$D_2^1(3)$	*a b c*	**I2**	a	$OH_w\cdots SO_4$	>b<c	$D_2^1(3)$	*a b c*
	b	$OH_c\cdots SO_4$	>b<d	$D_2^2(5)$			b	$OH_w\cdots SO_4$	>a<c	$D_2^2(5)$	
	c	$NH\cdots SO_4$	>b<e	$D_2^2(5)$			c	$OH_c\cdots SO_4$	>a<d	$D_2^2(5)$	
	d	$OH_w\cdots SO_4$	>c<e	$D_2^2(5)$			d	$NH\cdots SO_4$	>b<d	$D_2^2(5)$	
	e	$OH_w\cdots SO_4$	>b>a	$D_2^2(6)$			e	$OH_a\cdots O_w$	>c>e	$D_2^2(6)$	
			>c>a	$D_2^2(6)$					>d>e	$D_2^2(6)$	
			>a>d	$C_2^2(6)$					>a<b	$C_2^2(6)$	
			>a>e	$C_2^2(6)$					>c<d	$C_2^2(9)$	
			>d>e	$C_2^2(9)$					>a>e>a>e	$R_4^4(12)$	
			>b>c	$C_2^2(9)$					>b>e>b>e	$R_4^4(12)$	
Q1	a	$OH_a\cdots SO_3$	a	$C_1^1(8)$	*a b*	**Q2**	a	$OH_a\cdots SO_3$	>e<h	$D_2^1(3)$	*a b*
	b	$OH_c\cdots SO_3$	>b<c	$C_2^1(7)$			b	$OH_a\cdots SO_3$	>c>g	$D_2^2(4)$	
	c	$NH\cdots SO_3$	>b>a<b	$D_3^3(13)$			c	$OH_c\cdots O_w$	>c>h	$D_2^2(4)$	
			>c>a<c	$D_3^3(13)$			d	$NH\cdots SO_3$	<g>h	$D_2^2(5)$	
							e	$OH_c\cdots SO_3$	>a<f	$D_2^2(5)$	
							f	$NH\cdots SO_3$	>a<g	$D_2^2(5)$	
							g	$OH_w\cdots SO_3$	>b<d	$D_2^2(5)$	
							h	$OH_w\cdots SO_3$	>b<e	$D_2^2(5)$	
									>b<h	$D_2^2(5)$	
									>d<e	$D_2^2(5)$	
									>d<h	$D_2^2(5)$	
									>f<g	$D_2^2(5)$	
									<c>d	$D_2^2(8)$	
									<e>f	$D_2^2(8)$	
									>d>a	$D_2^2(10)$	
									>e>a	$D_2^2(10)$	
									>f>b	$D_2^2(10)$	
									>g>b	$D_2^2(10)$	
									>h>a	$D_2^2(10)$	
									>a>b	$C_2^2(16)$	

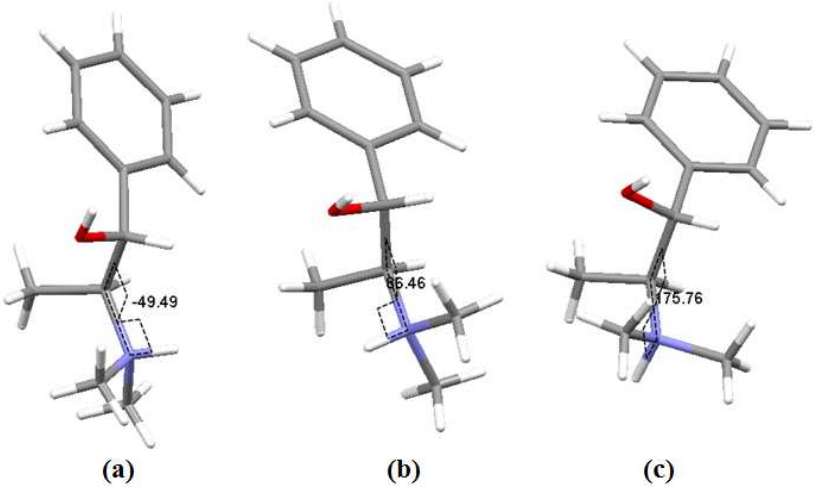
Supplementary Table S4: Graph-set analysis of dicarboxylate methylephedrinium salts

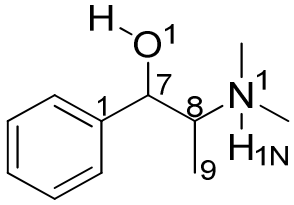
compound	hydrogen bond		graph-set		network growth	compound	hydrogen bond		graph-set		network growth
J1	a	$OH_c\cdots COO^-$	>a<b	$C_2^2(12)$	*a*	**J2**	a	$OH_c\cdots COO^-$	>a<b	$C_2^2(12)$	*a*
	b	$NH\cdots COO^-$					b	$NH\cdots COO^-$			
	c	$COOH\cdots COO^-$	c	$S_1^1(7)$			c	$COOH\cdots COO^-$	c	$S_1^1(7)$	
K1	a	$OH_c\cdots COOH$	>a<d	$D_2^2(7)$	*a*	**K2**	a	$OH_c\cdots COO^-$	>a<b	$C_2^2(7)$	*c*
	b	$NH\cdots COO^-$	>b<c	$D_2^2(7)$			b	$NH\cdots COO^-$	c	$S_1^1(6)$	
	c	$OH_c\cdots COOH$	<a>b	$D_2^2(8)$			c	$COOH\cdots COO^-$			
	d	$NH\cdots COO^-$	<c>d	$D_2^2(8)$							
	e	$COOH\cdots COO^-$	e	$S_1^1(6)$							
	f	$COOH\cdots COO^-$	f	$S_1^1(6)$							

Supplementary Table S5: Graph-set analysis of halide methylephedrinium salts

compound	hydrogen bond		graph-set		network growth	compound	hydrogen bond		graph-set		Network growth
L1	a	$OH_c\cdots X$	>a<c	$C_2^1(7)$	*b*	**L2**	a	$OH_c\cdots X$	>a<c	$C_2^1(7)$	*a*
	b	$NH\cdots X$					b	$NH\cdots X$			
M1	a	$OH_c\cdots X$	>a<c	$C_2^1(7)$	*b*	**M2**	a	$OH_c\cdots X$	>a<c	$C_2^1(7)$	*c*
	b	$NH\cdots X$	>a<c	$D_2^1(3)$			b	$NH\cdots X$			
P1	a	$OH_c\cdots X$	>a<d	$D_2^1(3)$	*a c*	**P2**	a	$OH_c\cdots X$	>a<c	$C_2^1(7)$	*b*
	b	$NH\cdots X$	>b<c	$D_2^1(3)$			b	$NH\cdots X$			
	c	$OH_c\cdots X$	>b<d	$D_2^1(3)$							
	d	$NH\cdots X$	>a<b	$C_2^1(7)$							
			>c<d	$C_2^1(7)$							

(1) Torsion angle values for the 3 observed configurations of the methylephedrine cation.





Torsion 1 = C1-C7-C8-N1

Torsion 2 = O1-C7-C8-C9

Torsion 3 = O1-C7-C8-N1

Torsion 4 = C7-C8-N1-H1N

Table S6: Torsion angles for compounds with molecular conformation (a)

Compound	Torsion 1	Torsion 2	Torsion 3	Torsion 4
L2	149.872	39.442	-87.019	-63.750
K2	152.215	41.116	-85.946	-60.656
M1	150.346	41.689	-86.154	-58.647
C1	149.013	39.084	-88.101	-57.001
Q1	140.838	30.205	-95.953	-56.404
K1	161.433	50.957	-76.283	-56.349
L1	150.079	41.890	-86.317	-54.145
B1	150.918	41.497	-85.932	-53.180
N2	157.020	46.982	-79.789	-52.887
D1(cation 2)	149.505	39.476	-87.017	-52.086
D2	147.528	37.301	-88.941	-51.315
A1	156.419	45.656	-81.266	-49.492
C2	154.518	44.596	-82.202	-49.194
K1	166.087	54.507	-72.200	-48.396
Q2(cation 1)	165.391	55.429	-71.385	-47.509
Q2(cation 2)	162.748	52.872	-73.438	-47.499
R1(cation 1)	162.837	53.898	-73.169	-46.931
E2	162.547	53.703	-73.391	-41.051
B2	164.576	55.473	-71.322	-40.880
O1	159.548	50.552	-76.479	-40.363
A2	162.641	54.041	-73.492	-37.712
O2	168.411	59.009	-67.802	-36.940
D1(cation 1)	179.895	69.027	-56.955	-26.273

Table S7: Torsion angles for compounds with molecular conformation (b)

Compound	Torsion 1	Torsion 2	Torsion 3	Torsion 4
F2	-175.094	69.728	-51.450	67.185
F1	-179.495	65.456	-55.561	69.316
H1(cation 1)	179.805	65.625	-56.731	76.266
R1(cation 2)	174.568	61.165	-60.587	76.628
P1(cation 1)	179.855	66.667	-56.348	76.802
P1(cation 2)	178.583	64.428	-58.010	77.093
P2	169.688	55.810	-66.166	79.544
I2	174.732	59.635	-62.003	80.721
G1(cation 2)	171.366	56.074	-65.766	85.091
G2	172.442	57.059	-63.687	86.032
M2	175.065	60.724	-61.287	86.227
H1(cation 2)	175.106	56.222	-63.692	86.455
H2(cation 2)	178.032	61.852	-59.303	87.031
H1(cation 3)	170.688	55.613	-65.791	87.465
H2(cation 1)	175.915	61.208	-60.639	88.783
J2	171.604	57.658	-64.081	91.288

Table S8: Torsion angles for compounds with molecular conformation (c).

Compound	Torsion 1	Torsion 2	Torsion 3	Torsion 4
T1	166.232	55.09	-70.734	175.646
N1	159.140	47.827	-77.711	175.759
S1	167.257	55.866	-69.320	179.575
E1	171.350	59.074	-66.444	-178.257
I1	166.268	54.510	-70.900	-176.816
J1	172.775	61.062	-64.363	-173.643
G1(cation 1)	-178.751	67.964	-56.612	-170.616

(2) Table of Melting Points and Densities.

Table S8: Melting points and density measurements for the 13 chemically identical enantiopure-racemic pairs. Melting points measured in triplicate, density from single crystal diffraction studies (e.g. at approx. 123K).

Compound	Density (g/cm^3)	Melting point (^{o}C)	Compound	Density (g/cm^3)	Melting point (^{o}C)
A1	1.320	131.7±0.06	A2	1.315	131.0±0.36
B1	1.348	80.1±2.46	B2	1.310	103.2±1.73
C1	1.295	138.2±0.61	C2	1.292	116.0±1.32
D1	1.296	167.1±0.68	D2	1.323	168.0±0.21
E1	1.222	100.7±0.98	E2	1.225	132.7±0.40
F1	1.274	111.1±2.35	F2	1.329	103.9±2.61
G1	1.322	102.2±2.87	G2	1.303	98.4±0.20
H1	1.274	not available	H2	1.331	not available
I1	1.360	82.4±1.11	I2	1.402	90.6±2.67
J1	1.259	125.7±0.55	J2	1.285	131.3±1.79
K1	1.271	113.6±0.20	K2	1.315	114.9±0.31
L1	1.422	177.0±0.93	L2	1.474	184.0±4.70
M1	1.241	194.0±0.91	M2	1.237	211.8±0.12

(3) Illustration of packing efficiency in 1,2-ethanedisulfonate and 2-nitrobenzoate salts.

The two pairs of salts, those of 1,2-ethanedisulfonate and 2-nitrobenzoate, have enantiopure compounds with considerable higher density values than their racemic counterparts, 1.46% and 2.90% respectively. For the 2-nitrobenzoate pair, Figure shows the unit cell voids, with probe radius of 0.5 Å and approximate grid spacing of 1.0 Å for the two salts. The racemic structure clearly shows more void area due to more inefficient packing that leads to the structure being considerably less dense than the chiral salt. The same principles apply to the 1,2-ethanedisulfonate salts, Figure.

Figure S1: Unit cell voids (1R,2S)(-)-methylephedrine 2-nitrobenzoate monohydrate (left) and (+/-)-methylephedrine 2-nitrobenzoate monohydrate (right)

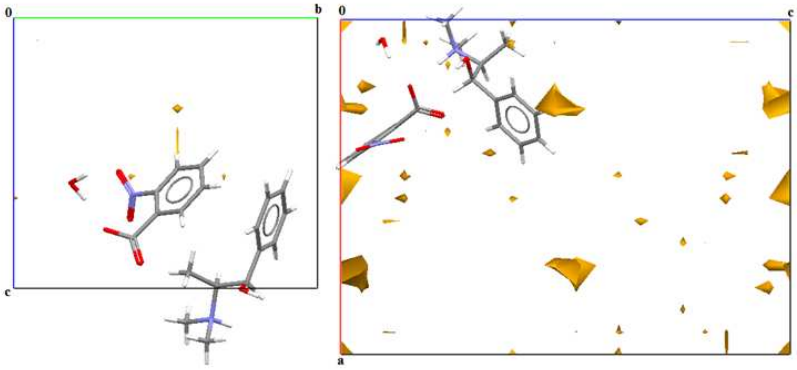


Figure S2: Unit cell voids (2R,3S)(-)-methylephedrine 1,2-ethanedisulfonate (bottom) and (+/-)-methylephedrine 1,2-ethanedisulfoante (top)