

Tunable Chiral Reaction Media Based on Two-Component Liquid Crystals: Regio-, Diastereo-, and Enantiocontrolled Photodimerization of Anthracenecarboxylic Acids

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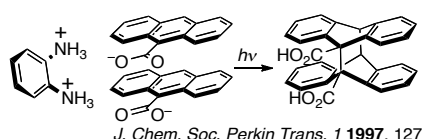
1. Introduction: Chemical Reactions in Ordered Media

- Ordered media can produce chiral environments.

=> asymmetric synthesis (e.g. photoreaction, which is unexplored in homogeneous media)¹

Crystals

- Highly ordered
- high selectivity
- low conversion



- #### Hosts in solution (e.g. micelles, bilayer, etc)
- Loose structure
 - low selectivity
 - high conversion

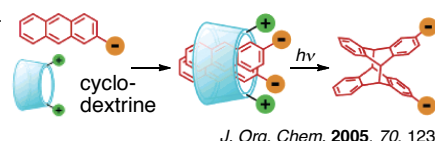


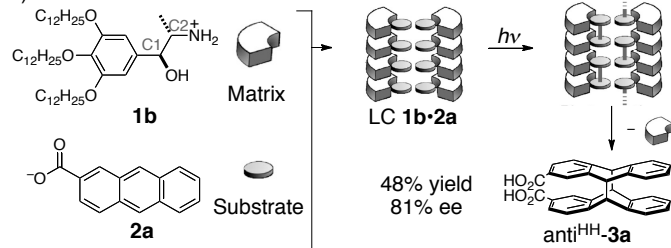
Figure 1. Conventional ordered medias and relationship between selectivity and reactivity in asymmetric synthesis.

- Liquid Crystals (LC): ordering close to crystals + molecular mobility
= highly selective asymmetric synthesis with good conversion
- however, no successful report due to poor molecular design and lack of mechanistic understanding

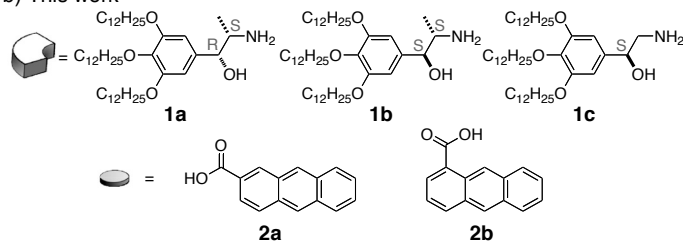
2. Previous Work: Enantioselective Photodimerization of Anthracene Derivative in Two-Component Liquid Crystal²

Scheme 1

a) Previous work



b) This work



- First asymmetric synthesis induced by a chiral liquid crystal
- Enantioselective photodimerization of anthracene **2a** was achieved in **1b•2a** liquid crystal.

This work: investigation of the effect of the stereochemistry of liquid crystal matrix in the asymmetric photodimerization of anthracenecarboxylic acids **2**

=> model for tunable chiral reaction media for carboxylic acids

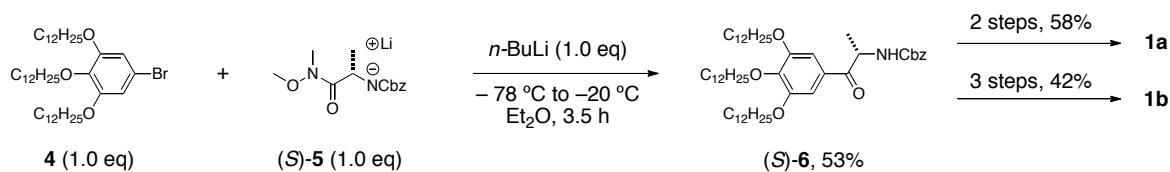
3. Tunable Chiral Reaction Media Based on Two-Component Liquid Crystal

3.1. Synthesis and Preparation of Liquid Crystal Salt

- Matrices **1a** and **1b** were synthesized from alanine derivative (*S*)-**5**.

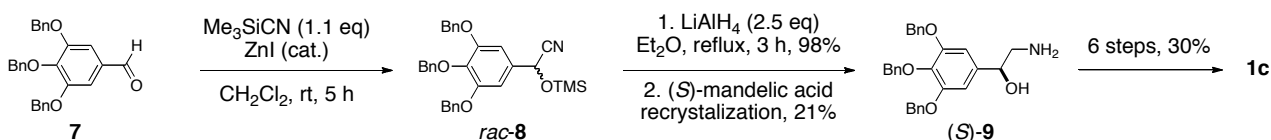
=> applicable to other amino acids = library of asymmetric matrices

Scheme 2. Stereocontrolled synthesis of the amphiphilic amino alcohol **1a** and **1b**.



• **1c** has only one chiral center => different strategy for the synthesis

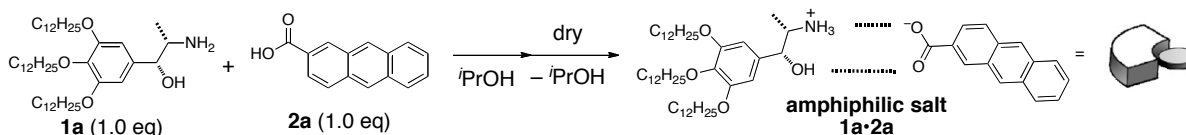
Scheme 3. Stereocontrolled synthesis of the amphiphilic amino alcohol **1c**.



• Salts were prepared from equimolar amounts of the amino alcohol and the carboxylic acid.

=> IR ($\text{C}=\text{O}$ absorbance): shift from $1680\text{--}1695\text{ cm}^{-1}$ to $1620\text{--}1650\text{ cm}^{-1}$

Scheme 4. Preparation of amphiphilic salt from amphiphilic amino alcohol **1a** and carboxylic acid **2a**.



3.2. Effect of Matrix Stereochemistry in the Structure of Amphiphilic Amino Alcohol Salts

• Characterization of thermotropic behavior of the salts => DSC, POM, XRD

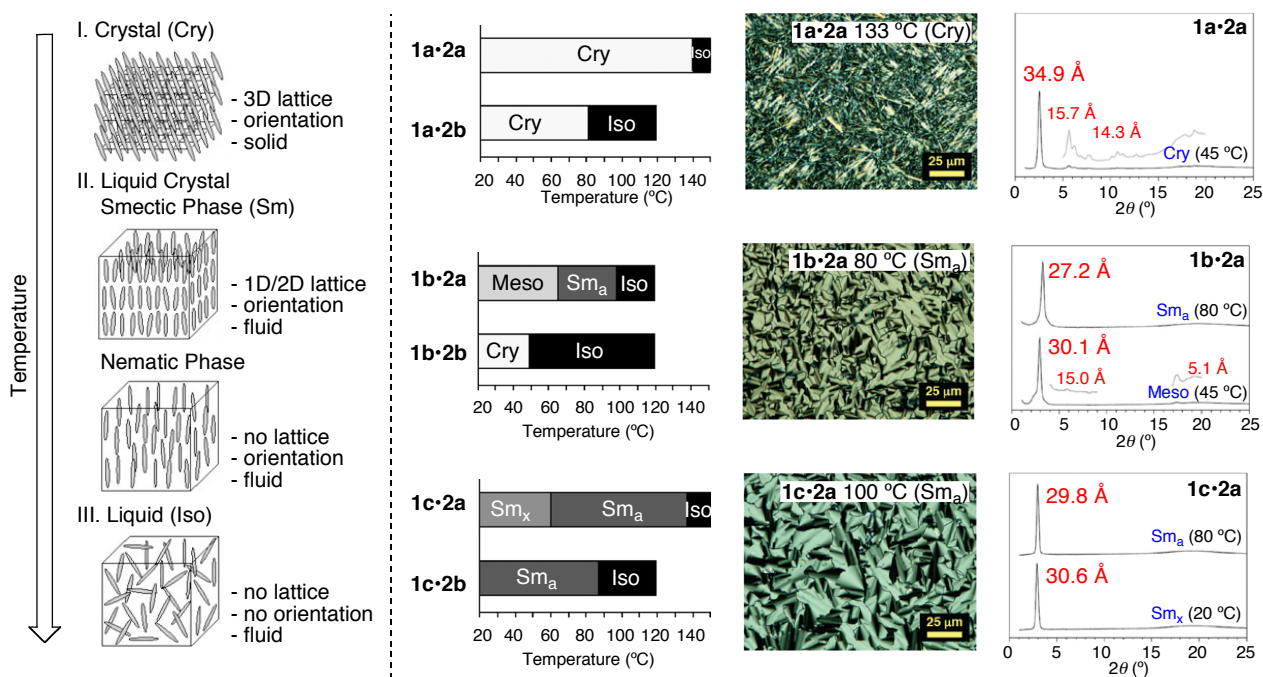


Figure 2. (a) Phases of a thermotropic liquid crystal. (b) Thermotropic behavior from differential scanning calorimetry (DSC), (c) polarized optical microscopy (POM) images, and (d) X-ray diffraction (XRD) patterns of the salts of amphiphilic amino alcohols with photoreactive carboxylic acids. (Cry: crystal, Iso: isotropic, Meso: unidentified mesophase, Sm_a: smectic A phase, Sm_x: smectic phase other than A).

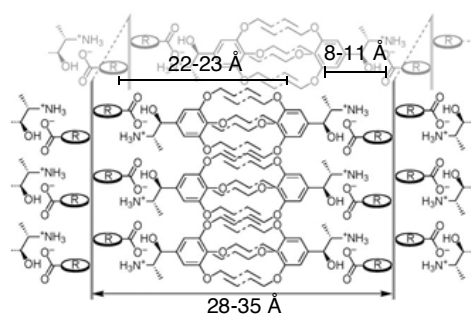


Figure 3. Schematic representation of amphiphilic amino alcohol and photoreactive carboxylic acid in a self-assembled bilayer.

- Different phase diagram for the salts prepared from **1a–1c**
 - unexpected result, since difference in the structure of the matrices represents less than 2% of total molecular weight
 - => different reactivities can be expected.
- Amphiphilic LC unit => bilayer structure
 - layer thickness d : $d_{\text{observed}} \text{ (XRD)} < d_{\text{calculated}}$
 - => interdigitation of alkyl chains

3.3. Photodimerization of Anthracenecarboxylic Acids (**2a** and **2b**)

- Photodimerization of anthracene derivatives (discovered in 1867)
 - = a benchmark for supramolecular systems in controlled reactions
- Dimerization of 2-anthracenecarboxylic acid (**2a**) in **1** gave 4 dimers.
 - = syn^{HH} , anti^{HH} , syn^{HT} , anti^{HT} (HH = head-to-head, HT = head-to-tail)

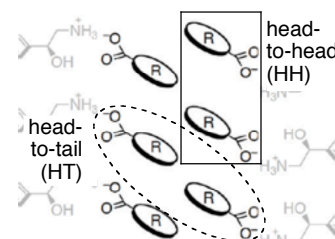


Figure 4. Formation of HH and HT dimers.

Table 1. Photodimerization of 2-Anthracenecarboxylic Acid (**2a**)

										R = CO ₂ Me	
2 x				$h\nu (>360 \text{ nm})$		$\text{Me}_3\text{SiCHN}_2$					
		2a		conditions		toluene/MeOH					
entry	medium	phase	temp. (°C)	time (h)	yield (%) ^a	product ratio (%) ^b					
						syn^{HH}	anti^{HH}	syn^{HT}	anti^{HT}	ee(%) ^b	anti^{HH}
1	1a	Cry	40	15	10	57	41	1	1		-15
2			80	15	23	52	44	2	2		-16
3		Iso	160	1	89	50	36	4	10		-14
4	1b	Meso	35	3	23	26	72	1	1		+78
5			35	15	58	27	71	1	1		+74
6			45	1	24	27	71	1	1		+86
7			45	3	48	28	70	1	1		+81
8			45	15	68	34	64	1	1		+67
9		Sm _a	80	1	72	46	52	1	1		+45
10			80	3	66	48	49	2	1		+26
11		Iso	110	1	83	52	45	2	1		+18
12	1c	Sm _x	40	3	42	56	42	1	1		+31
13			40	15	85	56	43	1	1		+32
14			105	1	64	61	37	1	1		+14
15			105	3	81	61	37	1	1		+16
16		Iso	160	1	91	56	41	2	1		+13
b	H ₂ O	Sol	25	1	88	7	14	36	43		n.d.
c	CH ₂ Cl ₂	Sol	25	2	96	21	7	22	32		n.d.

^a Determined by ¹H NMR. ^b Determined by HPLC. HH = head-to-head. HT = head-to-tail.

1. **Reactivity**: Iso > LC > Cry
 - Moderate reaction yields in LC were obtained after increase of the temperature/time.
2. **Regioselectivity**: HH > HT => intralayer dimerization
3. **Diastereoselectivity**: $\text{syn}^{\text{HH}}/\text{anti}^{\text{HH}}$ ratio was controlled by the amino alcohol stereochemistry
 - anti^{HH} selectivity (26:72) in **1b** and syn^{HH} selectivity (61:37) in **1c**
4. **Enantioselectivity** (anti^{HH}): very high in LC phases (up to 86%) but low in Iso phases
 - => originated from the framework of the chiral supramolecular structure

- Photodimerization of **2b**: moderate yields and high HH selectivity (Table 2)

Table 2. Photodimerization of 1-Anthracenecarboxylic Acid (**2b**)

entry	medium	phase	temp. (°C)	time (h)	yield (%) ^a	product ratio (%) ^b				ee(%) ^b anti ^{HH}
						syn ^{HH}	anti ^{HH}	syn ^{HT}	anti ^{HT}	
1	1a	Cry	25	15	55	75	22	2	2	-13
2		Iso	100	3	72	69	24	4	4	10
3	1b	Cry	25	15	39	47	40	10	3	-6
4		Iso	90	3	57	50	30	11	8	-8
5	1c	Sm _a	65	3	36	67	33	<1	<1	-9
6		Sm _a	65	15	43	66	34	<1	<1	-5
7		Iso	120	3	77	57	34	5	5	n.d.

^a Determined by ¹H NMR. ^b Determined by HPLC. HH = head-to-head. HT = head-to-tail.

- **Diastereoselectivity:** syn^{HH} > anti^{HH} / **Enantioselectivity (anti^{HH}):** low
=> in anti^{HH}-**3b**, the carboxylic acid groups are too far to form in the 1D hydrogen-bond network in LC

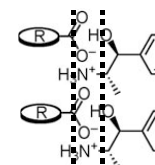


Figure 5. Network of hydrogen bond.

3.4. Characteristic Properties of Amphiphilic Amino Alcohols

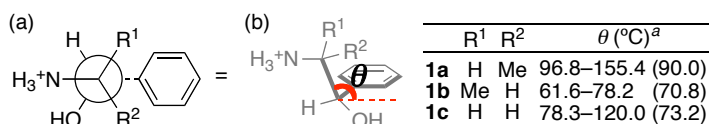


Figure 6. (a) Newman projection of the conformation of the amino alcohols. (b) Definition of the dihedral angle θ . ^a Range determined by structure of 20 analogous amino alcohols obtained from Cambridge Structure Database (optimized value, HF/6-31G).

- Dihedral Angle θ = angle between amino/hydroxy and aromatic planes
- defines the environment formed by LC
- different θ = different reactivity
- **1b** has the narrowest θ range

=> rigid structure, high enantioselectivity

3.5. Mechanism (Figure 7)

- Photodimerization of anthracenecarboxylic acid
 - (a) reduction of distance in z-axis
 - (b) expansion in x-axis to avoid congestion of the alkyl chains (observed by XRD)
- Flexible structure and strong matrix-substrate interaction suppressed the collapse of the ordered structure of LC.

=> high stereoselectivity with high conversion

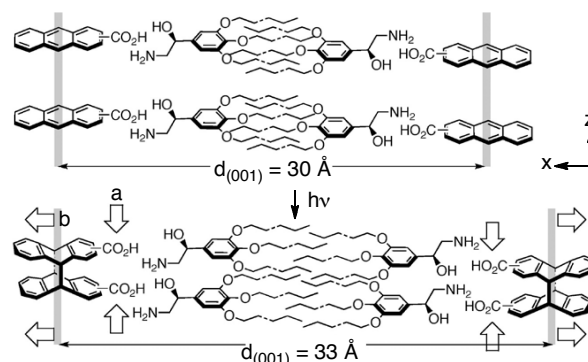


Figure 7. Schematic representation of the plausible structural changes of **1c·2a** through the photodimerization of **2a**.

4. Conclusion

Small changes in the liquid crystal matrix structure resulted in changes in the supramolecular structure, turning possible the tuning of stereoselectivity in the reaction product.

References

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2. Ishida, Y.; Kai, Y.; Kato, S.; Misawa, A.; Amano, S.; Matsuoka, Y.; Saigo, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 8241–8245.