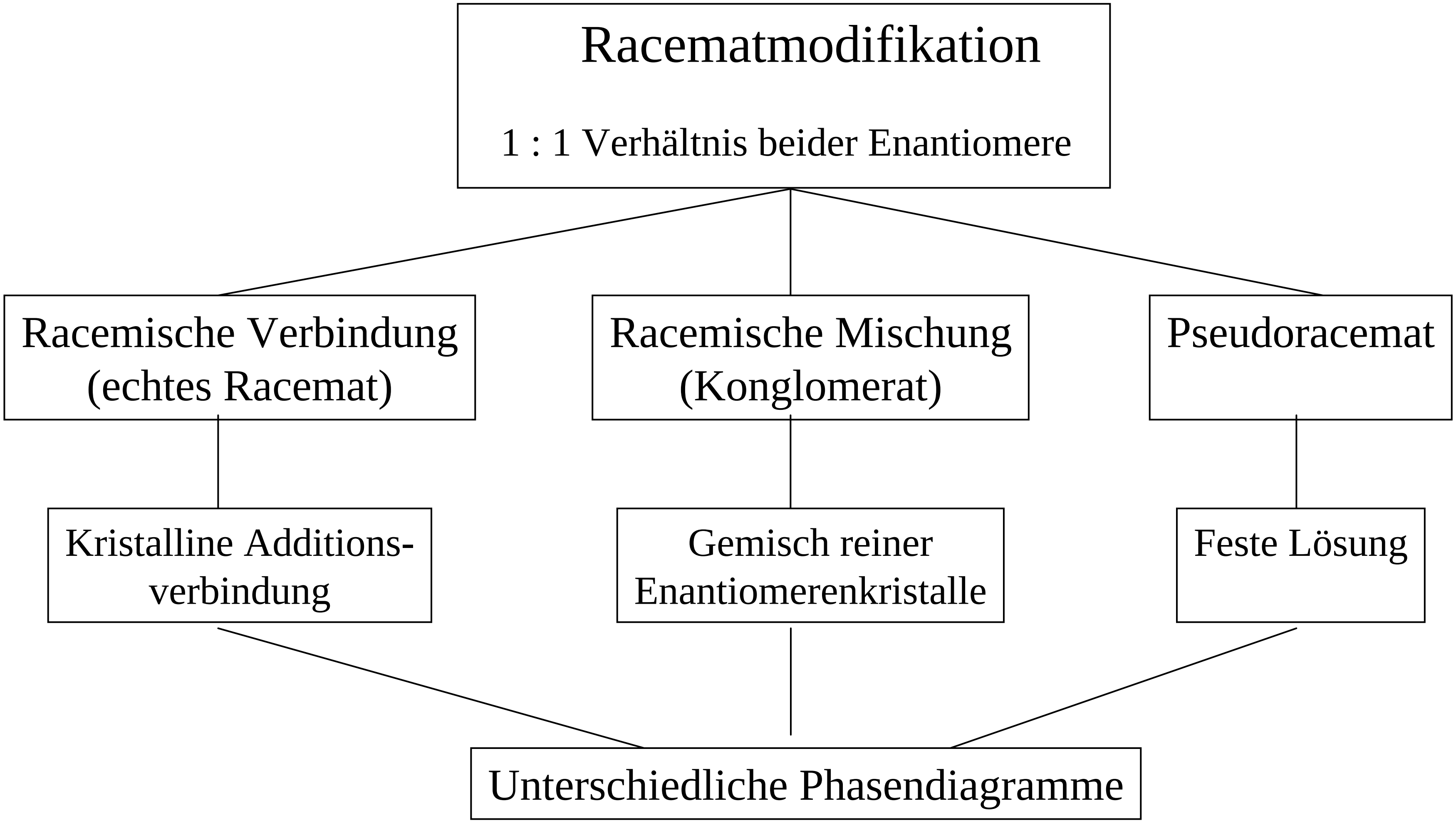
GEFTA-Fortbildungskurs „Praxis der Untersuchung von Phasenübergängen“
Ansbach, 30./31.10.2001

Phasendiagramme von Enantiomeren

Dr. Steffen Neuenfeld, Zentrale Verfahrensentwicklung

MERCK



Racematmodifikation

1 : 1 Verhältnis beider Enantiomere

Racemische Verbindung (echtes Racemat)

Racemische Mischung (Konglomerat)

Pseudoracemat

Kristalline Additionsverbindung

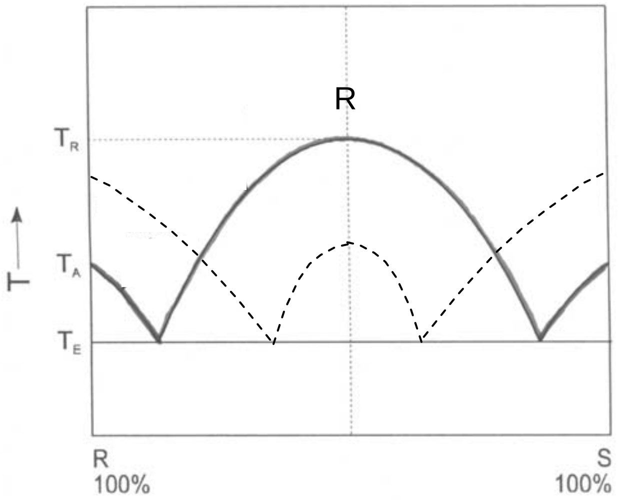
Gemisch reiner Enantiomerenkristalle

Feste Lösung

Unterschiedliche Phasendiagramme

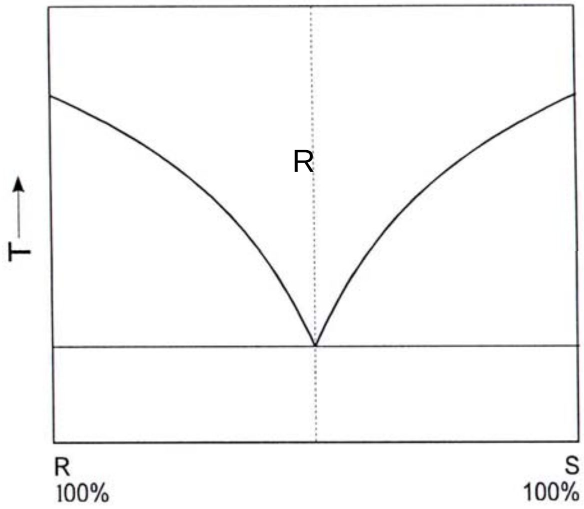
Racematmodifikationen

Racemische Verbindung (echtes Racemat)



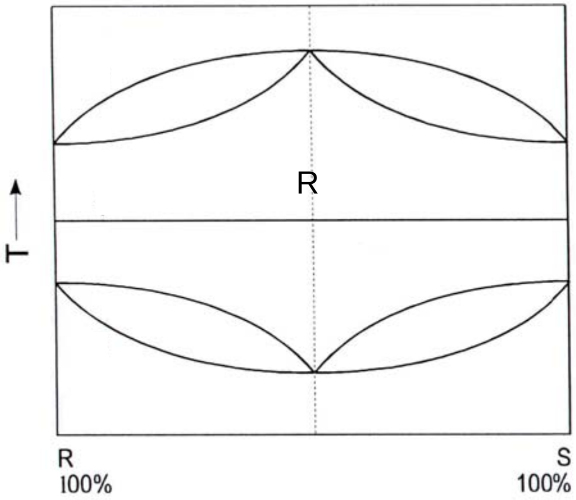
RSRSRSRS
RSRSRSRS
RSRSRSRS
RSRSRSRS
RSRSRSRS

Racemische Mischung (Konglomerat)



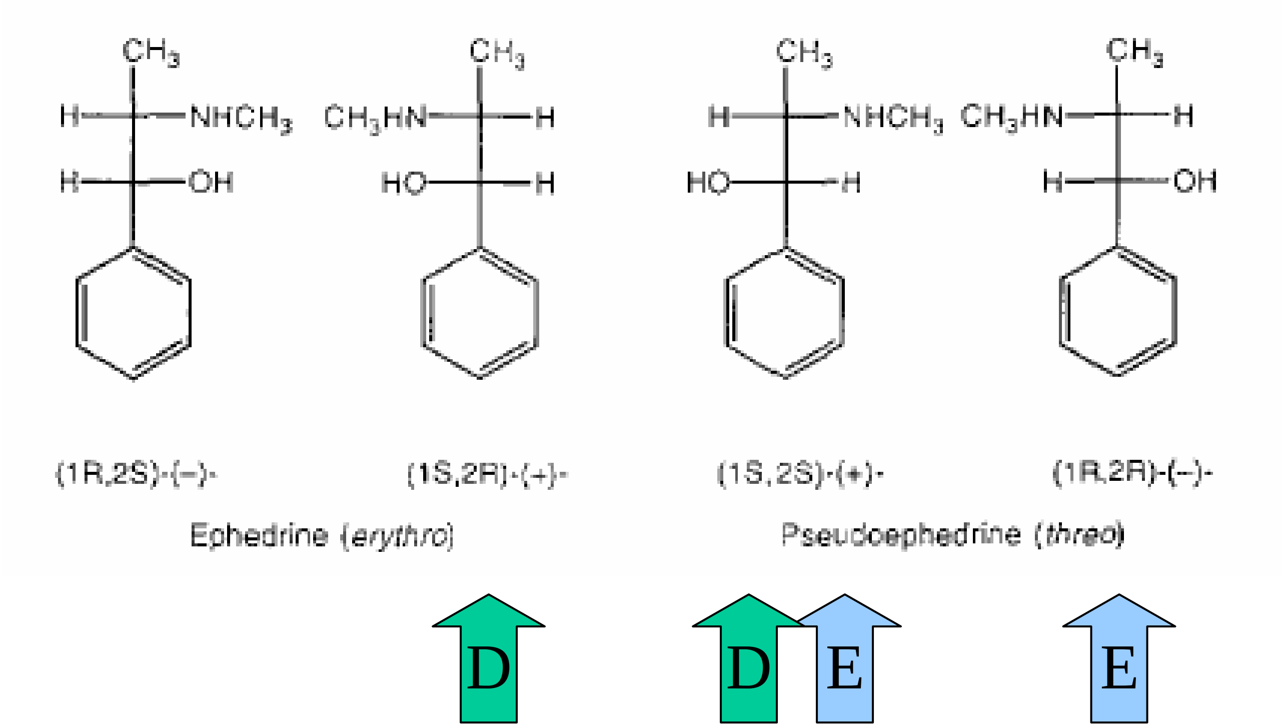
RRRRRRR
RRRRRRR
RRRRRRR
RRRRRRR
RRRRRRR

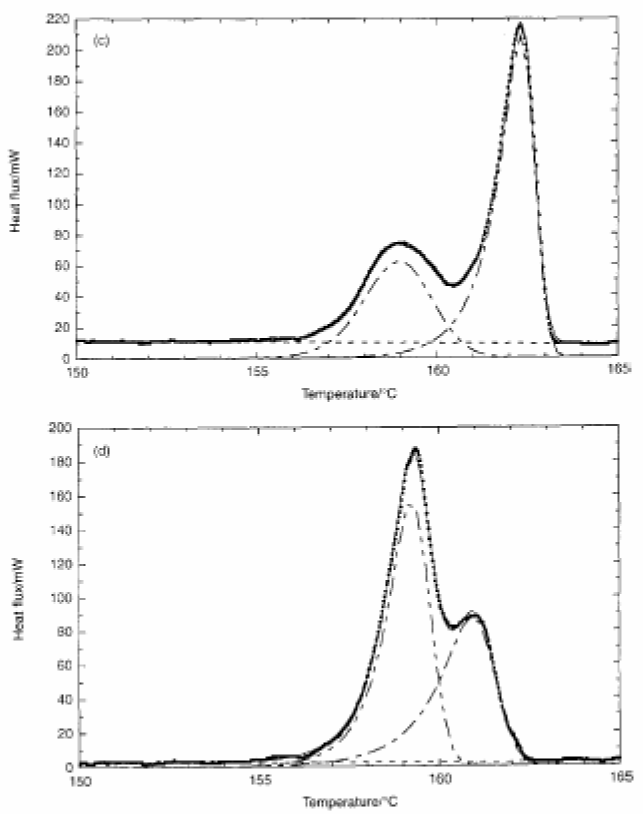
Pseudoracemat



RRSSRRR
SRRRRSS
RRRRRSR
RSSSRRR
RSRSRRS

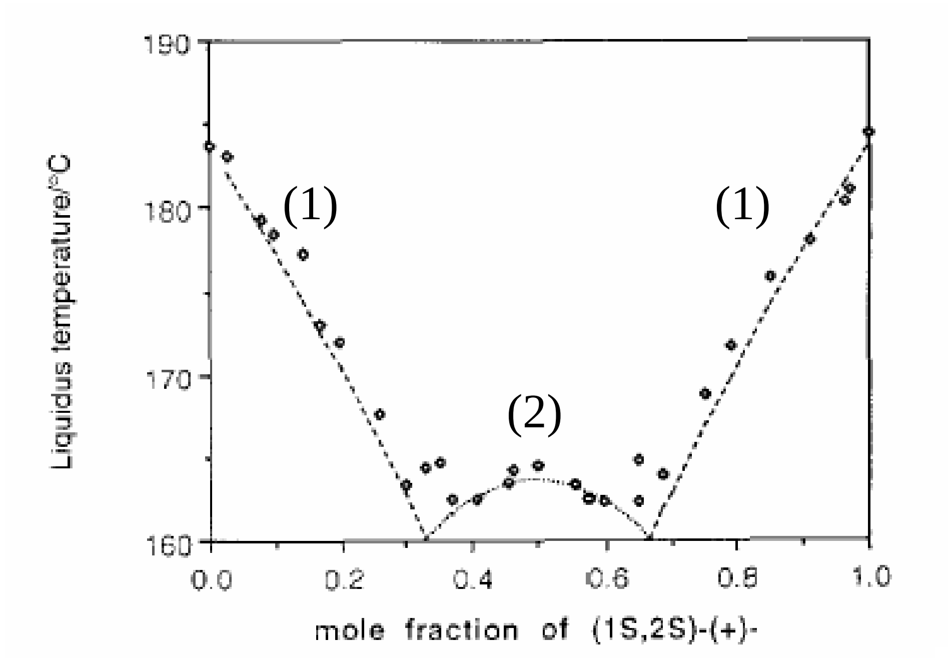
Phasengleichgewichte zwischen Ephidrine HCl-Enantiomeren und Diastereomeren

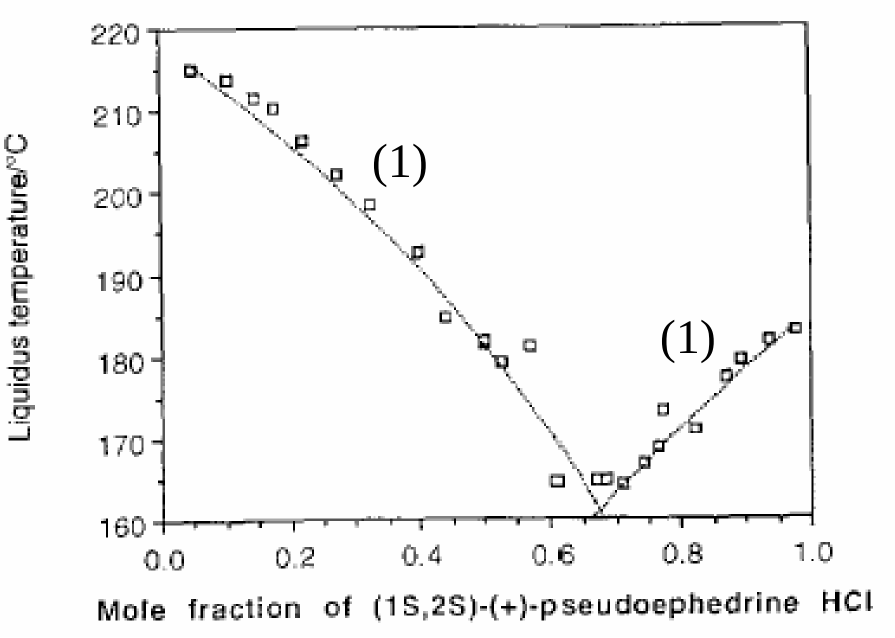

CH3
H
NHCH3
OH
CH3HN
HO
(1R,2S)-(–)-
(1S,2R)-(+)-
(1S,2S)-(+)-
(1R,2R)-(–)-
Ephedrine (erythro)
Pseudoephedrine (threo)
D
D
E
E



Quelle: Prankerd, R.J.P.; Elsabee, M.Z.: Thermochim. Acta 248 (1995) 147-160

Phasengleichgewichte zwischen Ephidrine HCl-Enantiomeren und Diastereomeren





Anpassung: Schröder-van Laar-Gleichung (1)

$$\ln x_1 = \frac{\Delta_{fus} H_A}{R}\left(\frac{1}{T_A} - \frac{1}{T}\right)$$

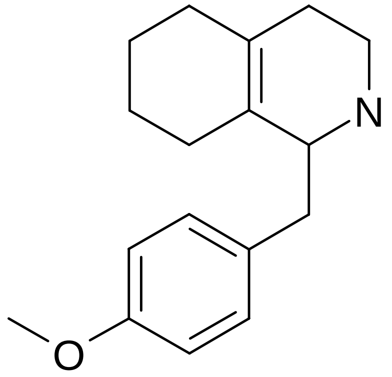
Prigogine-Defay-Gleichung (2)

$$\ln 4x_1(1-x_1) = \frac{2\Delta_{fus} H_R}{R}\left(\frac{1}{T_R} - \frac{1}{T}\right)$$

Quelle: Prankerd, R.J.P.; Elsabee, M.Z.: Thermochim. Acta 248 (1995) 147-160

Phasengleichgewichte zwischen Enantiomeren von MOHIC-Salzen

MOHIC-Base



1-(4-Methoxy-benzyl)-1,2,3,4,5,6,7,
8-octahydro-isoquinoline

Maleat - Racemische Verbindung

Fp. (Enantiomer)	137°C
Fp. (Racemat)	134°C
Fp. (Eutektikum)	124°C

Acetat - Konglomerat

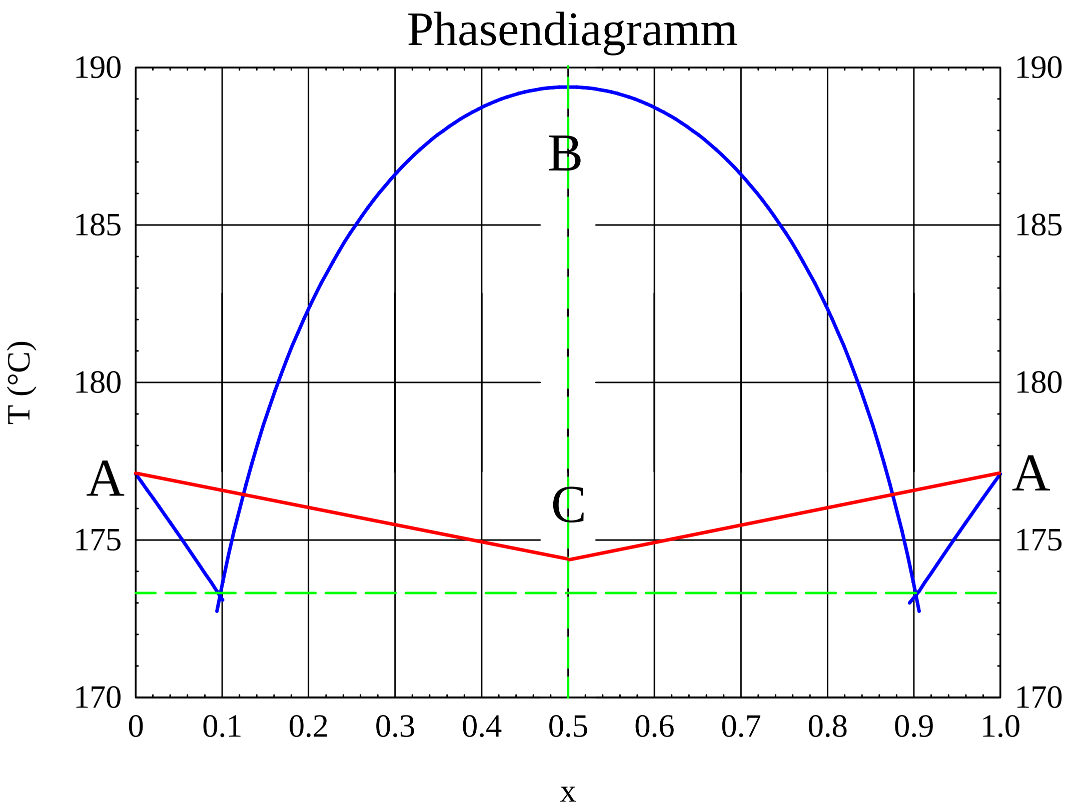
Fp. (Enantiomer)	89°C
Fp. (Konglomerat)	72°C

Hydrochlorid und Benzoat

Umwandlung von Konglomerat zu racemischer Verbindung während der DSC-Messung

Quelle: interner Merck-Report 1984

Polymorphie bei Racematen
Beispiel - EMD 96717



A - Enantiomere - Fp. 177°C
B - Racemische Verbindung - Fp. 189°C
C - Racemisches Konglomerat - Fp. 175°C

IR-Spektrum und XRD für A und C gleich

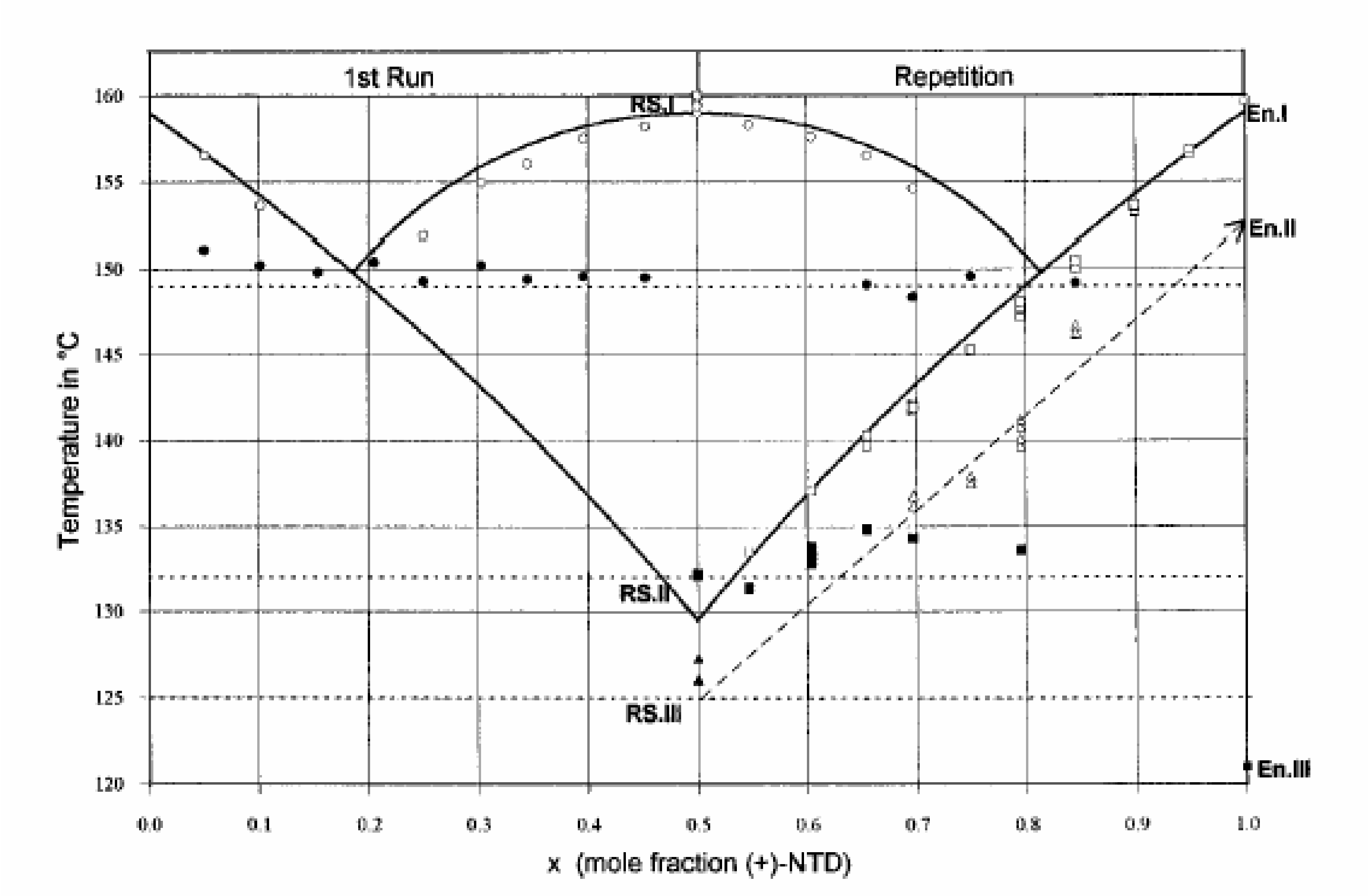
Löslichkeit B < C

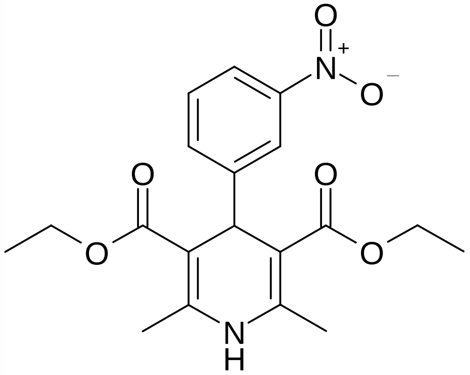
Freie Enthalpie für Bildung aus Enantiomeren

$\Delta_R G$ (B) = -3.8 kJ/mol

$\Delta_R G$ (C) = 0

Polymorphie bei Racematen
Beispiel - (R)- und (S)-Nitrendipine





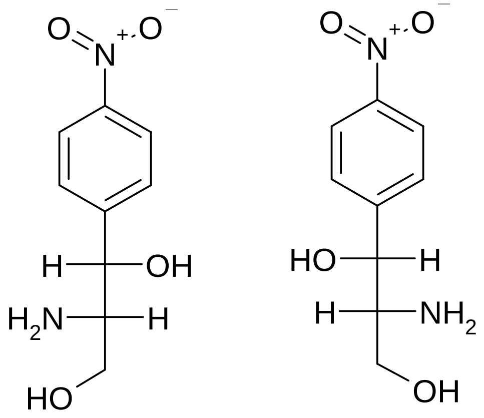
DSC-Messungen

⇩

3 Racematformen
2 polymorphe Enantiomere
+ ein weitere vorausgesagt

Quelle: Burger, A.; Rollinger, J.M.; Brüggeller, P.: J. Pharm. Sci. 86 (1997) 674-679

Bestimmung der Enantiomerenreinheit



2-Amino-1-(4-nitro-phenyl)-propane-1,3-diol

Phasendiagramm = Konglomerattyp

Enantiomer	Fp. 164.8°C	$\Delta_f H = 46.22$ kJ/mol
Konglomerat	Fp. 141.9°C	$\Delta_f H = 42.56$ kJ/mol

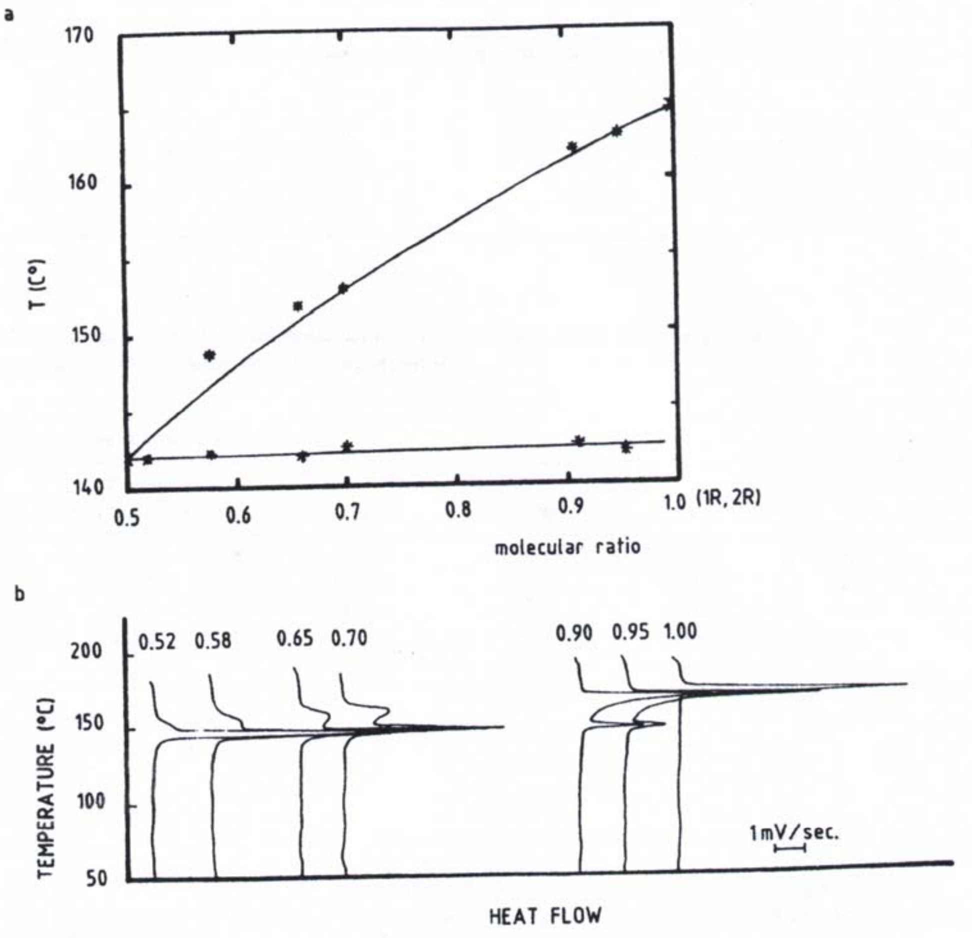


Fig. 2: Melting point phase diagram a of **2** in the molecular ratio 0.5 - 1.0 calculated by *Schröder-Van Laar*[7] equation with experimental points (*) obtained by DSC heating curves b.

Quelle: Pitre, D.; Nebuloni, M.; Ferri,V.: Arch. Pharm. (Weinheim) 324 (1991) 325-328

Bestimmung der Enantiomerenreinheit

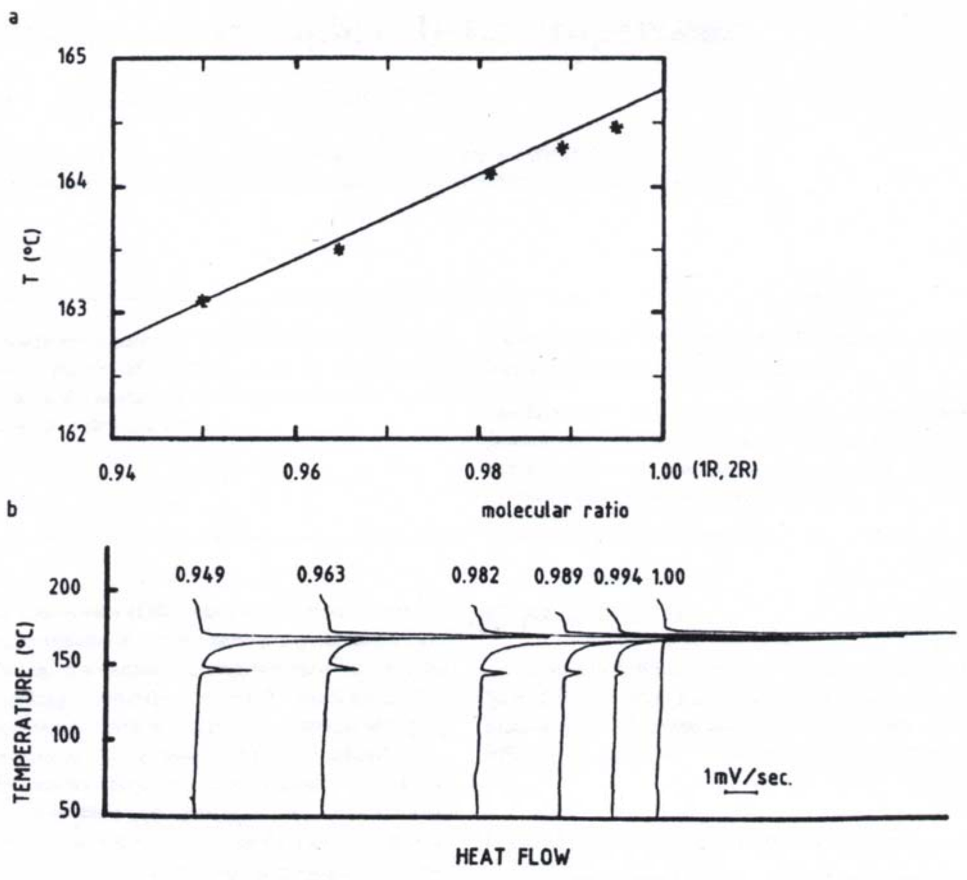


Fig. 3: Melting point phase diagram a of 2 in the molecular ratio 0.94 - 1 calculated by *Schröder-Van Laar*[7] equation with experimental points (*) obtained by DSC heating curves b.

Enantiomerenreinheit

Kalibrierkurve zwischen Reinheit 95 % und 100 %

Vergleich

Fp. (°C)		Enantiomerenreinheit (%)	
gemessen	berechnet	DSC	Polarimetrie
163.10	163.0	97.45	97.47
163.61	163.5	98.62	98.65
164.16	164.1	99.01	99.08
164.44	165.3	99.41	99.49
164.61	164.4	99.66	99.45

Quelle: Pitre, D.; Nebuloni, M.; Ferri,V.: Arch. Pharm. (Weinheim) 324 (1991) 325-328