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Study of the Mechanism of the Optical Resolution of N-methylamphetamine via Diastereoisomeric Salt Formation by the Pope-Peachey Method

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Abstract: During the optical resolution of racemic N-methylamphetamine by half an equivalent of R,R-tartaric acid in the presence of half an equivalent of hydrochloric acid the tartrate salt of the R-base precipitates with a low optical purity. The optical purity of the precipitated salt is increased by enantiomer exchange between the solid and solvent phase.

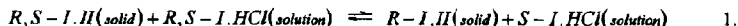
During optical resolutions of racemates diastereoisomeric salts are formed where the diastereoisomers are usually separated by fractional crystallization¹. On reproduction of these resolution processes it is sometimes very hard to achieve the same results as in the original experiments. This is why: "Yet many practitioners believe that there is a mystique and an aura of "art" to resolutions."² Knowing the mechanism of a process the mystique disappears. In this paper we report an investigation of an optical resolution of which the reproductivity was problematic. Racemic N-methylamphetamine (I)³ can be resolved by the Pope-Peachey method⁴ using half an equivalent of R,R-tartaric acid (II) and half equivalent of hydrochloric acid⁵. For the systematic investigation three parallel experiments were made for five different crystallization times. We tried to ensure exactly the same conditions for each experiment⁶. The tartrate and hydrochloride content⁷ of the precipitated salt and the optical rotation of the recovered base⁸ were measured in each experiment. The results are summarized in Table 1.

Table 1. Experimental results⁵

Crystallization time		Precipitated salt g	Tartrate content of the precipitated salt w/w %	Hydrochloride content of the precipitated salt w/w %	$[\alpha]_D^{20}$	Optical purity % average
15 minutes	1.	0.986	45.34	1.46	-5.02	25.13
	2.	0.966	45.09	1.34	-5.30	25.66
	3.	0.983	45.27	1.43	-5.10	27.41
90 minutes	1.	1.005	46.08	1.21	-4.75	26.56
	2.	0.895	45.83	0.96	-4.85	28.04
	3.	0.972	46.26	1.33	-5.18	26.98
5 hours	1.	0.882	45.77	0.97	-5.02	26.56
	2.	0.965	46.88	0.92	-6.86	36.29
	3.	0.990	46.83	0.96	-5.09	26.93
24 hours	1.	0.970	46.14	0.99	-6.46	34.13
	2.	0.997	46.92	0.91	-6.04	31.96
	3.	0.973	46.36	1.04	-5.72	30.26
115 hours	1.	0.863	45.98	0.94	-7.80	41.27
	2.	0.953	46.25	0.99	-5.62	29.73
	3.	0.961	45.98	1.14	-10.46	55.34

† decreased

The weights of precipitated salts and their tartrate content were approximately the same in each experiment, indicating that nearly all tartrates precipitated immediately⁹. The optical purity of the precipitated salt was quite low in the beginning, at longer times the optical purity of the precipitates definitely increased, proving that there is an enantiomer exchange between the precipitated salt and the hydrochloride salt. The R-I enantiomer accumulated in the solid phase, as R-I.II salt¹⁰, while in the mother liquor the S-I.HCl accumulated (Equation 1.)



When the experiments were repeated at vigorous stirring for 90 minutes, the precipitated salt had 54.57 % optical purity. Our experiments indicate that during an optical resolution the process of precipitation can be kinetically controlled and for an efficient resolution it may be important to provide an opportunity for the formation of the thermodynamically controlled salt.

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References and Notes

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- 2.) Jacques, J.; Collet, A.; Wilen, S.H. Enantiomers, Racemates and Resolutions, Wiley and Sons, New York, 1981, 378.p.
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- 5.) 7.84 g (0.0525 mol) racemic N-methylamphetamine and 9.73 g (0.0525 mol) racemic N-methylamphetamine hydrochloride were dissolved in 70 ml of abs. ethanol and 7.91 g (0.0525 mol) R,R-tartaric acid in 56 ml of abs. ethanol. Both stock solutions were divided into fifteen portions by volume by a burette and reacted at 22±1°C. The mixtures were standing undisturbed for 15, 90 minutes and 5, 24, 115 hours, than the precipitates were filtered and dried. From 0.4 g of each salt the base was liberated by cNaOH and extracted from the aqueous phase by dichloromethane.
- 6.) All experiments were performed at the same work-bench at 22±1°C room temperature. Stock solutions of the racemate and the resolving agent were used to avoid the error of weight measurements. All the flasks used had identical size and shape.
- 7.) The tartrate and hydrochloride content of the salts were determined by potentiometry by a RADIOMETER-85 TTT automatic titrator with 0.1 N NaOH and 0.1 N AgNO₃.
- 8.) The specific rotations was measured by a Perkin Elmer 241 polarimeter. The specific rotation of the optically pure R-N-methylamphetamine is $[\alpha]_D^{20} = -18.90$ (c 0.1; 1N HCl).
- 9.) The salts were not washed at filtering. The small amount of hydrochloride found in the salts probably comes from the mother liquor sticked and dried to the surface of the salt.
- 10.) This is in accordance with the results³, that the R-I II is the more stable salt than S-I.II.

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