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A QUANTITATIVE APPROACH TO OPTICAL RESOLUTION

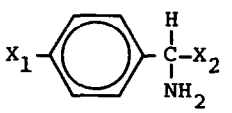
Elemér Fogassy, Antal Lopata[1], Ferenc Faigl, Ferenc Darvas[1], Mária Ács, László Tőke*

Department of Organic Chemical Technology, Technical University, 1111 Budapest, Müegyetem rkp. 3, Hungary
[1]Institute for Coordination of Computer Techniques, 1368 Budapest, POB 224, Hungary

Significant statistical relationships have been found between the parameters characterizing the results and circumstances of the resolutions of seventeen phenylglycine derivatives. The successful predictions given for the results of six independent resolutions prove the utility of these relationships.

Since its inception in 1848, the Pasteur type resolution has remained to this day the most important method for obtaining optical antipodes from racemates, for example [1,2]. No rules, however, have been enunciated to assist in predicting the specific enantiomer which will crystallize in the form of a diastereomeric salt, or the percentage in which it will be obtained. We propose to present here a model to fill this lacuna. In the model, both the resolution results and the experimental circumstances are characterized by suitable parameters, which have to be measured for a sufficient number of resolutions so that we can examine the relationships between the two sets of variables, using the method of linear regression analysis.

In order to demonstrate the model, we have carried out statistical analyses on the resolution data for the phenylglycine derivatives I. The resolutions were accomplished by using equimolar amounts of L-tartaric acid in different solvents, starting with solutions of optimal concentrations giving the highest yields. In all cases but one, that being the amide derivative, the salt of the D enantiomer crystallized out of solution.

(I) 

where X_1 = H, OH, OMe, Cl; X_2 = CN, $CONH_2$, COOMe, COOEt

The resolution results have been characterized by the parameter S calculated by using the equation $S = kt$, where k is the yield of the diastereomer salt taken as 1.00 if half the racemate has been separated in crystalline form, and t is the optical purity of the base derived from that salt, with its sign

taken as positive if the enantiomer crystallizing out belongs to the D series.

The factors influencing $\underline{S}$ are the structure of the starting racemate, the characteristics of the solution, and the structure of the chiral agent. In the present instance, this last factor is kept constant so that it need not be considered.

It is known that secondary bonds such as hydrogen and hydrophobic bonds, as well as charge-transfer and van der Waals interactions, can have a decisive influence on the results of a resolution [3], thus when characterizing the structure of a racemate, they must be considered in the first place. The problem is quite similar to that arising when examining the relationships between chemical structures and biological activities, where for the characterization of the secondary bond-forming character playing an important part in the pharmacon-receptor interaction, parameters obtainable from physicochemical (thermodynamic, kinetic) models are mainly used [4,5]. Using such parameters, the effect of the structure of racemates on $\underline{S}$ has been taken into account by considering the hydrophobic, polar, and steric effects of substituents X_1 and X_2 for the compounds of type I. We have thus used Fujita and Hansch's hydrophobic π constant [6], Swain and Lupton's inductive F and mesomeric R polar parameters for aromatic substituents [6], Taft's σ^* polar parameter for aliphatic substituents, calculated from $\sigma^* = 1.38F + 0.14R$ [7], and the molar refraction index MR describing the steric bulk and the van der Waals bond-forming character of substituents [6]. The effect of the solvent on salt formation has been considered by characterizing its polarity by means of the empirical polarity factor E_T [8].

Taking $\underline{S}$ as dependent variable and π_1, F_1, R_1, MR_1, π_2, σ_2^*, MR_2, E_T as independent variables, we have carried out linear regression analysis [9] for the seventeen resolutions listed in rows 1-17 of the Table, and have obtained equations with good statistical characteristics. Though these equations offer several alternatives to explain the relationships between the results and the circumstances of resolutions, they do not differ from each other essentially. As an example, we show the best four of them:

	$\underline{n}$	$\underline{r}$	$\underline{F}$	$\underline{s}$
(1) $\underline{S} = 0.517\pi_2 + 2.280\sigma_2^* - 0.015E_T - 0.001$	17	0.967	63	0.140
(2) $\underline{S} = 0.524\pi_2 + 2.082\sigma_2^* - 0.016E_T + 0.017MR_1 + 0.107$	17	0.971	50	0.137
(3) $\underline{S} = 4.374\sigma_2^* + 0.107MR_2 - 0.014E_T - 2.529$	17	0.964	57	0.147
(4) $\underline{S} = 4.183\sigma_2^* + 0.110MR_2 - 0.015E_T + 0.021MR_1 - 2.461$	17	0.970	48	0.140

where $\underline{n}$ is the number of observations, $\underline{r}$ is the correlation coefficient, $\underline{F}$ is the value of Fischer's test, and $\underline{s}$ is the residual error. The statistical reliability of each equation is higher than 99.9 %.

The equations show that the order of importance of the factors influencing the resolution results is the following: the role of substituent directly connected to the chiral center is the most important, the polarity of solvent used

has less influence, and the effect of substituent on the phenyl ring is nearly negligible. This seems to be a chemically intelligible result. Another conclusion is that an increase in the bulkiness of the substituent X_1, and an increase in the bulkiness, the hydrophobic and electron attracting character of the substituent X_2 will help crystallization of the salt of the D enantiomer. Thus, the equations predict that the amide group at the second substituent site, having very hydrophilic and little electron attracting character as well as relatively small bulkiness, will induce the salt of the L enantiomer to crystallize. Similarly, it is the L enantiomer that is more likely to crystallize in a more polar solvent. This effect is in accordance with the statement given in the literature that solvent polarity will not only influence, but can also determine the crystallization pathway [10,11].

Table Resolution data. Experiments in rows 1-17 were utilized in the statistical analyses, in rows 18-23 are predictions.

resolution circumstances									resolution results				
racemate		solvent	parameters						product			parameter	
X_1	X_2		MR_1	π_2	F_2	R_2	MR_2	E_T	config.	yield k	purity t	S exp.	S calc.
H	COOMe	MeOH	1.03	-0.01	0.33	0.15	12.87	55.5	D[a]	0.26	0.62	0.16	0.12
H	COOMe	EtOH	1.03	-0.01	0.33	0.15	12.87	51.9	D[a]	1.20	0.27	0.32	0.17
H	COOEt	MeOH	1.03	0.51	0.33	0.15	17.47	55.5	D[a]	0.50	0.97	0.48	0.62
H	COOEt	EtOH	1.03	0.51	0.33	0.15	17.47	51.9	D[a]	0.72	0.97	0.70	0.68
H	$CONH_2$	H_2O	1.03	-1.49	0.24	0.14	9.81	63.1	L[b]	0.86	-0.85	-0.73	-0.86
H	$CONH_2$	Me_2CO	1.03	-1.49	0.24	0.14	9.81	42.2	L[b]	0.95	-0.80	-0.76	-0.54
H	CN	H_2O	1.03	-0.57	0.51	0.19	6.33	63.1	D[b]	0.95	0.15	0.14	0.34
H	CN	Me_2CO	1.03	-0.57	0.51	0.19	6.33	42.2	D[b]	1.20	0.78	0.94	0.66
H	CN	PhMe	1.03	-0.57	0.51	0.19	6.33	33.9	D[b]	1.50	0.48	0.72	0.79
OH	COOMe	MeOH	2.85	-0.01	0.33	0.15	12.87	55.5	D[a]	0.76	0.24	0.18	0.15
OH	CN	EtOAc	2.85	-0.57	0.51	0.19	6.33	38.1	D[c]	0.81	0.90	0.73	0.76
OMe	CN	H_2O	7.87	-0.57	0.51	0.19	6.33	63.1	D[b]	0.80	0.60	0.48	0.48
OMe	CN	MeOH	7.87	-0.57	0.51	0.19	6.33	55.5	D[b]	0.88	0.71	0.62	0.60
OMe	CN	EtOH	7.87	-0.57	0.51	0.19	6.33	51.9	D[b]	0.83	0.73	0.61	0.66
OMe	CN	Me_2CO	7.87	-0.57	0.51	0.19	6.33	42.2	D[b]	0.90	0.88	0.79	0.80
OMe	CN	PhMe	7.87	-0.57	0.51	0.19	6.33	33.9	D[b]	1.60	0.60	0.96	0.93
Cl	COOMe	MeOH	6.03	-0.01	0.33	0.15	12.87	55.5	D[a]	0.28	0.85	0.24	0.22
OMe	$CONH_2$	MeOH	7.87	-1.49	0.24	0.14	9.81	55.5	L[b]	0.74	-0.83	-0.61	-0.60
OMe	$CONH_2$	Me_2CO	7.87	-1.49	0.24	0.14	9.81	42.2	L[b]	0.70	-0.82	-0.57	-0.40
OMe	$CONH_2$	H_2O	7.87	-1.49	0.24	0.14	9.81	63.1	L[b]	0.92	-0.76	-0.70	-0.72
H	$CONH_2$	MeOH	1.03	-1.49	0.24	0.14	9.81	55.5	L[b]	0.75	-0.85	-0.64	-0.75
H	CN	MeOH	1.03	-0.57	0.51	0.19	6.33	55.5	D[b]	0.60	0.90	0.54	0.46
H	CN	EtOH	1.03	-0.57	0.51	0.19	6.33	51.9	D[b]	0.65	0.89	0.58	0.51

[a]ref.no. 12, [b]ref.no. 13, [c]ref.no. 14

The utility of the equations was verified by comparing the predictions for the outcome of six resolutions not involved in the original statistical calculations (in rows 18-23 of the Table), with the experimental values. These comparisons show that each equation is able to predict not only the enantiomer, the salt of which crystallizes out first, but also the yield within an experimental error of ± 17 %. The predictions given by equation (4) are shown in the Table.

Summarizing our results, it can be stated that there are mathematically describable relationships between the results and the circumstances of resolutions. Within the series of compounds I, equations (1-4) can describe the dependence of the results of resolutions performed by using equimolar amounts of L-tartaric acid, starting with solutions of optimal concentrations, upon the structure of racemate and the polarity of solvent used. As to the calculations, the resolution results are primarily influenced by the structure of racemate, the polarity of solvent does not have a decisive role in this case.

References:

[1] Optical Resolution Procedures of Chiral Compounds (ed. by Paul Newman), Resolution Information Center, New York, (1978)

[2] E. Fogassy, M. Ács, and J. Gressay, Periodica Politechnica 20(2), 219 (1976); E. Fogassy, M. Ács, J. Felméri, and Zs. Aracs, Ibid. 20(3), 247 (1976)

[3] S.H. Wilen, "Topics in Stereochemistry (ed. by N.L. Allinger, E.L. Eliel)", Vol. 6, p. 107, Wiley Interscience, New York, (1971)

[4] C. Hansch, R.M. Muir, T. Fujita, P.P. Maloney, F. Geiger, and M. Streich, J. Am. Chem. Soc. 85, 2817 (1963)

[5] Y.C. Martin, Quantitative Drug Design, Vol. 8 in Medicinal Research Series, Marcel Dekker, New York, (1978)

[6] C. Hansch, A. Leo, S.H. Unger, K.H. Kim, D. Nikaitani, and E.J. Lien, J. Med. Chem. 16, 1207 (1973)

[7] C.G. Swain, and E.C. Lupton, J. Am. Chem. Soc. 90, 4328 (1968)

[8] K. Dimroth, C. Reichardt, T. Siepmann, and F. Bohlmann, Liebigs Ann. Chem. 661, 1 (1963)

[9] N.R. Draper, and H. Smith, Applied Regression Analysis, John Wiley, New York, (1966)

[10] K. Patterson, Ark. Kemi. 7, 279 (1954)

[11] B. Sjöberg, Ark. Kemi. 9, 295 (1956)

[12] J.C. Clark, H.G. Phillips, M.R. Steer, J. Chem. Soc. Perkin Trans. I., 1976, 471 and 475 (1976)

[13] E. Fogassy, F. Faigl, experimental works in publication

[14] Hung. Patent No. 154 410 (Aug. 11, 1972, Chinoin Pharmaceutical and Chemical Works, J. Schawarcz)

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