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A NEW METHOD FOR DESIGNING OPTICAL RESOLUTIONS AND FOR DETERMINATION OF RELATIVE CONFIGURATIONS

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Abstract—A new method has been elaborated for designing optical resolutions via diastereoisomeric salt formation, based upon the principle of three point interaction. In our method the favourite resolving agent to a given racemate and suitable resolution method can be found, and it can be predicted which enantiomer is expected in excess in the crystallized diastereoisomeric salt.

The most frequent way of getting chiral molecules in optically active form is optical resolution via diastereoisomeric salt formation. The enantiomer separation is based upon the differences in physico-chemical properties of the formed diastereoisomers. There have been only few successful attempts for solving special problems in the field of designing different reactions resulting in optically active compounds, i.e. predicting the chiral agent to a given substrate, the solvent, the molar ratio, etc. (See Prelog's rule,[1] Horeau's rule,[2] the Ugi–Ruch model,[3] Quantitative Approach to Optical Resolution.[4]) Therefore we have tried to elaborate a good and easy to treat theory for designing new resolution procedures.

During the reaction of two mirror image molecules (F and ꟻ) and an optically active reagent (resolving agent: R) two diastereoisomeric compounds (FR and ꟻR) can be derived, as is seen in Fig. 1a. A Newman-like projection is more suitable to illustrate the possible interactions (Fig. 1b). The axis is the dotted line in Fig. 1a.

Let the d—f bond be the strongest, first order interaction (e.g. salt formation between NH_2 and COOH groups), then the most probable conformer is the one in which the a, b, e and i, h, g ligands are in the most favorable positions regarding the electronic and steric factors. Let us suppose that more than one second order interaction can be formed in both diastereoisomers. Let the a–i interaction be the first among them. This can be generated in both diastereoisomers. So far there is still no difference between the two molecules, but the third interaction must be necessarily different, because of the mirror image relation of the enantiomers (see the principle of three point interaction).[17]

Differences between diastereoisomers are based upon the existence or hindrance of the third attachment. The second order bonds can be of either attractive (hydrogen-bridge, charge-transfer interaction) or repellant character. In case ring systems, the connection between components of the formed diastereoisomers is oriented by the plane-like parts of the molecules.

We have examined a number of resolutions via diastereoisomeric salt formation. Results of resolutions are characterized by the parameter S [S = yield (%) × optical purity (%) × 10^{-4}].[4]

The line of analysis is as follows: As Fig. 1a shows the molecules are approached from the direction of the salt forming groups. The possible conformers of the newly formed diastereoisomeric salt pairs were selected by using Dreiding models. After having selected the assumed second order interactions, we have ranked these possible interactions by the use of empirical electronic parameters (we have employed the Taft's σ^* values).[5] Then the σ^* values of interacting groups were summed ($\Sigma\sigma^*$) for the single diastereoisomers. Subtracting the $\Sigma\sigma^*_{FR}$ from the $\Sigma\sigma^*_{\text{ꟻ}R}$ one can obtain $\Delta\Sigma\sigma^*$, characterizing the difference between the physico-chemical properties of diastereoisomers (Eq. 1).

$$|\Sigma(\sigma^*_{j\text{ꟻ}} + \sigma^*_{jR}) - \Sigma(\sigma^*_{jF} + \sigma^*_{jR})| > 0 \qquad (1)$$

"j" is a variant depending on the number of interacting groups, although in fact the difference is derived from the $\Delta\Sigma\sigma^*$ of the third interaction. Indices F, ꟻ and R are the symbols of enantiomers and resolving agent, respectively.

In the case of compounds having two or more chiral

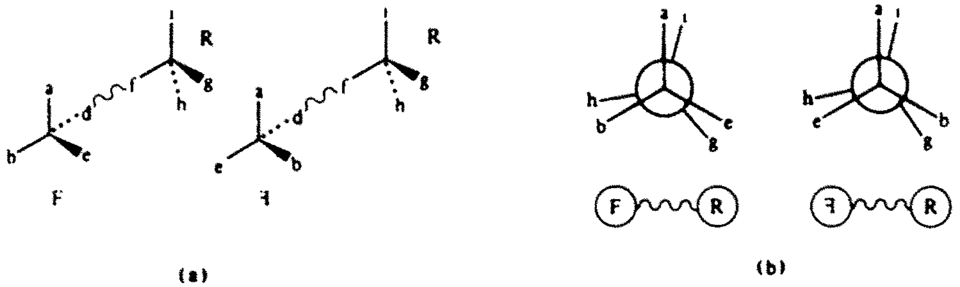


Fig. 1.

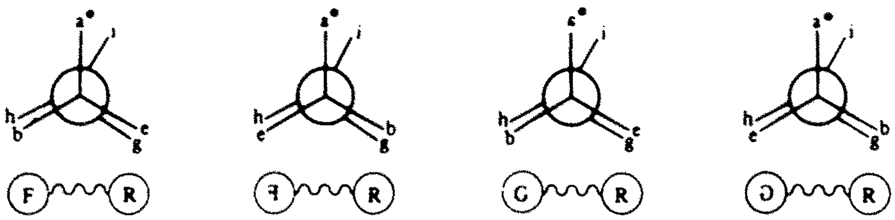
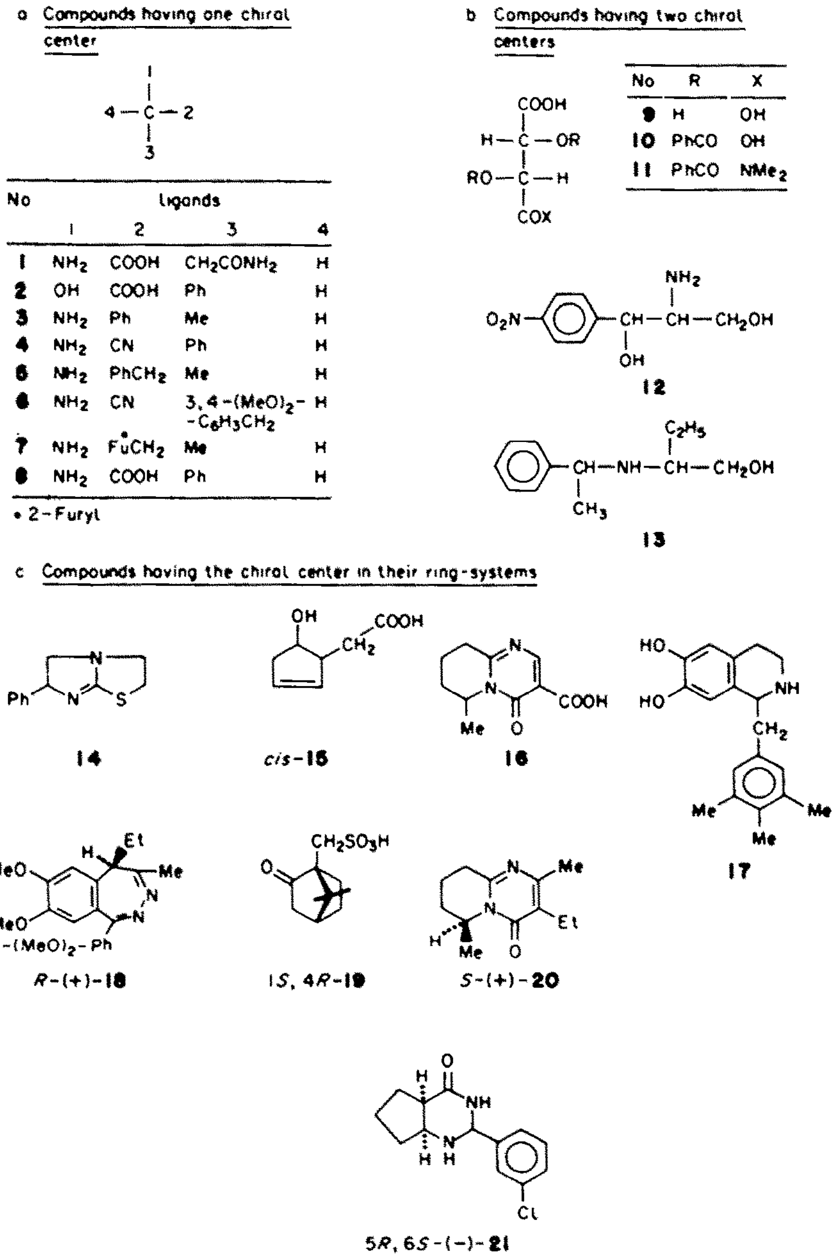


Fig. 2.

centres, the *S* for the racemates are not identical. Let F–Ⅎ be in diastereoisomeric relation with G–Ↄ racemate (resolving agent: R). Newman-like projections of the formed diastereoisomers are seen in Fig. 2. a* is the mirror image of ɐ*. It can be seen that if $\Sigma\sigma\mathrm{F_R}$ is larger than the $\Sigma\sigma\Finv_{\mathrm{R}}$, then $\Sigma\sigma\mathrm{G_R}$ is also larger than $\Sigma\sigma\Game_{\mathrm{R}}$. As there is a difference between a* and ɐ*, the behaviour of FR and GR must be different, too.



No	Ligands 1	2	3	4
1	NH$_2$	COOH	CH$_2$CONH$_2$	H
2	OH	COOH	Ph	H
3	NH$_2$	Ph	Me	H
4	NH$_2$	CN	Ph	H
5	NH$_2$	PhCH$_2$	Me	H
6	NH$_2$	CN	3,4-(MeO)$_2$-C$_6$H$_3$CH$_2$	H
7	NH$_2$	Fu*CH$_2$	Me	H
8	NH$_2$	COOH	Ph	H

* 2-Furyl

No	R	X
9	H	OH
10	PhCO	OH
11	PhCO	NMe$_2$

Scheme 1.

Table 1. Results of resolutions grouped by the employed method

No.[ref.]	Racemate	Resolving agent	Enantiomer in excess in precip.	S	$1+\lg S$	$\Delta\Sigma\sigma^*$	Differences in interactions
I. Molar ratio of racemate to resolving agent = 1 : 1, solvent water							
1[6]	4	R,R-9	S-(−)	0.140	0.1461	0.410	Ph...HO
2[7]	16	R,R-12	R-(−)	0.408	0.6107	0.661	$CONH_2$...HO
3[8]	1	R,R-10	S-(−)	0.489	0.6893	0.657	$CONH_2$...PhCOO
4[6]	6	R,R-9	R-(+)	0.455	0.6580	0.598	OCH_3...HO
5[9]	17	R,R-9	S-(−)	0.593	0.7731	0.621	OH...HO
II. Molar ratio of racemate to resolving agent = 1 : 0.5, solvent water							
1[6]	2	R,R-12	R-(−)	0.385	0.5855	0.410	OH...Ph
2[7]	16	R,R-12	R-(−)	0.459	0.6618	0.661	$CONH_2$...HO
3[10]	15	R-3	S,S-(−)	0.478	0.6794	0.410	OH...Ph
4[11]	14	R,R-10	S-(−)	0.673†	0.8280	0.811	$(Ph...PhCOO)_2$
5[12]	17	R,R-9	S-(−)	0.794	0.8998	0.621	OH...HO
6[8]	1	R,R-10	S-(−)	0.813	0.9101	0.657	$CONH_2$...PhCOO
7[13]	12	R,R-11	S,S-(−)	0.852	0.9304	0.617	OH...PhCOO
8[14]	8	1S,4R-19	R-(−)	0.800	0.9030	0.946	CO...HOOC
III. Molar ratio of racemate to resolving agent = 1 : 0.5, solvent water–water immiscible organic solvent							
1[6]	5	R,R-10	R-(−)	0.267	0.4265	0.405	Ph...PhCOO
2[15]	7	R,R-9	S-(+)	0.309	0.4900	0.576	Fu‡...HOOC
3[15]	7	R,R-10	S-(+)	0.500†	0.6990	0.811	(Fu‡...PhCOO)$_2$
4[16]	18	R,R-10	R-(+)$_{major}$	0.400	0.6021	0.594	CH_3O...PhCOO
5[6]	15	R-3	S,S-(−)	0.532	0.7259	0.410	OH...Ph
6[11]	14	R,R-10	S-(−)	0.670†	0.8221	0.811	$(Ph...PhCOO)_2$
7[6]	6	R,R-9	R-(+)	0.737	0.8675	0.598	CH_3O...HO
8[6]	13	R,R-10	S,S-(−)	0.470	0.6721	0.410	Ph...PhCOO

† Neutral salt precipitates.

‡ The σ^{*}_{Fu} value is taken equal to the σ^{*}_{Ph}.

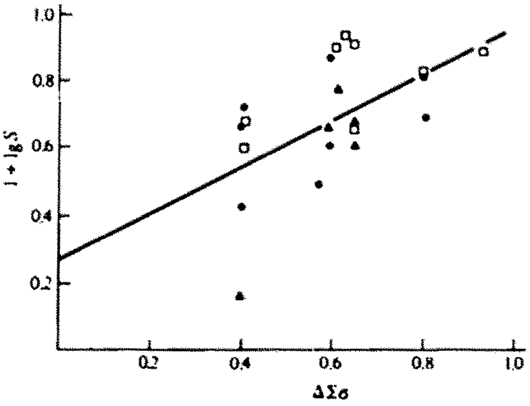


Fig. 3. Plot of the linearized relationship of Eq. 3 (made clearer by plotting the straight line of 21 data points). ▲, Method I; □, method II; ●, method III.

Method		I	II	III
Number of data	21	5	8	8
Standard deviation	0.1924	0.2470	0.1364	0.1525
α	0.7105	2.19	0.4665	0.3944
β	0.2698	−0.715	0.5005	0.4359

Consequently, such a resolution can be accomplished where only one of the four isomers will be crystallized.[6] If the difference is not large enough for a complete separation, the simultaneous precipitation of FR and GR is expected. Their ratio depends upon $\Sigma\sigma^{*}_{FR} - \Sigma\sigma^{*}_{GR}$.

We have compared the results of a number of resolutions accomplished in water. The examined compounds are listed in Scheme 1, in three groups according to the employed methods.

According to our results, the change of parameter S can be considered as a function of $\Delta\Sigma\sigma^{*}$ (Eq. 2).

$$S = f(\Delta\Sigma\sigma^{*}). \qquad (2)$$

The relationship can be linearized in the following manner

$$1 + \lg S = \alpha\Delta\Sigma\sigma^{*} + \beta \qquad (3)$$

"α" and "β" are constants, characterizing the resolution method, "α" is the sensitivity of the given method. It is noteworthy that Eq. 3 represents a Hammett-like relationship, in which S is the enantiomer in excess in the crystallized diastereoisomeric salts related to half the amount of the initial racemate. Data of the resolutions involved in our calculations are summarized in Table 1. We have plotted $1 + \lg S$ versus $\Delta\Sigma\sigma^{*}$, in different methods (Fig. 3).

In all of the examined cases—the diastereoisomer for which the calculated $\Sigma\sigma^{*}$ was larger crystallized from the employed polar solvent. This fact and Eq. 3 give the possibility of predicting the relative configuration of the enantiomer which is in excess in the precipitated salt if the resolving agent's configuration is known (or *vice versa*).

The configuration at C-5 of **18** benzodiazepine (controlled by X-ray), at C-6 of **20** pyrido-pyrimidine, C-2 of **7** furyl-iso-propylamine and C-5, C-6 of **21** cyclopentanopyrimidine have been determined using our method.

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