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The Synthesis, QSAR, and Molecular Modeling of Pyrazolone Magenta Couplers

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Abstract

A synthetic strategy was devised whereby the activity (D-max) of pyrazolone couplers could be manipulated by structural variations of the 3-substituent (the ballast) of the ring. This work describes both qualitative and quantitative structure-activity relationships, along with the use of a mathematical model, for predicting the pyrazolone's activity. The use of molecular modeling to understand the importance of an internal hydrogen-bonding conformation to the activity and dye hue will also be shown.

Introduction

The propensity for pyrazolone heterocycles to form magenta dyes upon reaction with oxidized phenylene diamine is highly dependent on the nature of the heterocylic ring substituents. In state-of-the-art film systems, it is important to be able to control the dye-forming reaction of 2-equivalent pyrazolone couplers in order to obtain images with good color reproduction and low granularity. For reversal films, this requires a coupler with relatively low activity. It was found that pyrazolone couplers with alkylthio and arylthio coupling-off groups in the 4-position were too low in activity to be useful in reversal systems, and those with aryloxy coupling-off groups had poor raw-stock keeping due to oxidative instability. Derivatives with heterocyclic nitrogen coupling-off groups, such as pyrazole were typically too high in activity. A synthetic program was initiated to delineate structural features of the pyrazole substituted pyrazolone couplers that would bring the activity closer to that of 4-equivalent analogs and achieve desirable granularity in a reversal film format.

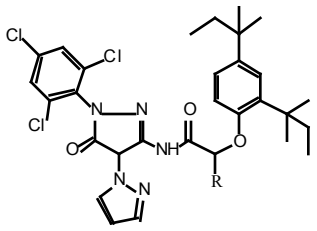
Results and Discussion

The activity of two-equivalent, pyrazolone couplers can be manipulated by structurally modifying the ballast. These effects were studied by examining the hydrophobic, steric, and conformational properties of the ballast group. The couplers synthesized for this study were coated in a single-layer, fast magenta emulsion, half-molar with respect to the 4-equivalent pyrazolone reference coupler. They were processed through the standard E-6 process with a 4 minute first developer step. The maximum densities were read and normalized to the standard reference coating to enable realistic comparisons between coating sets. The term "activity" will be used throughout this report to refer to this normalized D-max measurement.

Effect of Hydrophobicity on Activity

A series of couplers was prepared to examine the effect of hydrophobicity on photographic activity. The physical parameter chosen to describe the degree of hydrophobicity was the log of the partition coefficient for octanol/water. Calculated values (ClogP) were obtained using the molecular modeling program, SIMS[1] version 1.4.

To define the limits of the hydrophobic effect, five couplers, differing in the length of the alkyl side chain, were prepared. The side chains were straight chain alkyl groups, which did not provide significant steric hindrance due to their flexible nature. Thus, the observed changes primarily reflected differences in hydrophobicity. As seen in Fig. 1, the C4 and C6 analogs were quite active and not useful for reversal films. The C8, C12, and C16 analogs were much lower in activity but not significantly different from each other. Thus, increasing the hydrophobicity of the coupler did decrease the activity, but only to the point where apparent full partitioning into the coupler solvent was achieved. Further decreases in activity required additional structural modifications such as the incorporation of sterically hindering groups.



		ClogP	D-Max
1	R = C_4H_9	7.9	1.2
2	R = C_6H_{13}	9.0	1.0
3	R = C_8H_{17}	10.1	0.8
4	R = $C_{12}H_{25}$	12.2	0.8
5	R = $C_{16}H_{33}$	14.3	0.8

Figure 1. Defining the limits of the hydrophobic effect.

Steric Effects

A ballast with an additional phenyl group between the pyrazolone and the ballast of 4 might be expected to increase the logP and possibly shift the hue bathochromic. However, when this derivative, 6 was prepared, it unexpectedly exhibited the opposite effect! The D-max increased and the hue underwent a 4 nm hypsochromic shift! It was clear that factors other than the degree of hydrophobicity of the ballast were responsible for the low activity of 4.

Comparison of the structures of 4 and 6 revealed that the additional phenyl ring in the 6 ballast increased the distance between the bulky *tert*-pentyl groups and the

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coupling site. If the *tert*-pentyl groups were exerting a steric influence on the coupling reaction, then increasing the steric bulk by incorporating highly branched *tert*-octyl groups should further lower activity. Thus, 7 was prepared and found to have significantly decreased activity compared to 4. To eliminate increased hydrophobic character as a contributing factor, 7 was compared to 5 (C16 side chain) with similar ClogP. Coupler 7 still showed a relative decrease in normalized D-max of 36%. This was attributed to increased steric hindrance inhibiting the formation of the tetrahedral leuco-dye intermediate.

A more stringent test of this hypothesis was the comparison of 4 and 8 which differ only in replacing *tert*-pentyl groups for n-pentyl groups. The solubility properties (ClogP) of the two couplers were essentially equivalent. The electronic properties of n-pentyl versus *tert*-pentyl, as measured by sigma para,[2] were also comparable. However, the flexible n-pentyl groups of 8 did not provide as much steric hindrance as the branched *tert*-pentyl groups of 4, resulting in a more active coupler.

It was not immediately obvious why structural changes on the phenoxy ring, at a distance of more than six atoms from the coupling site, would have such a profound effect on the coupling activity. This prompted an investigation of the three-dimensional structural properties of pyrazolone magenta couplers.

A rendering of a CPK model of the tetrahedral intermediate of 4 showed considerable crowding of the van der Waals surfaces of the ballast and the pyrazole coupling-off group. The additional phenyl ring in the ballast of 6 extends the steric components further from the coupling site. Consequently, there was a larger "pocket" for a more facile formation of the tetrahedral leuco intermediate and a resultant 50% increase in coupler activity. This is consistent with the conclusions made from studies on the hydrophobic effect. Hydrophobic couplers, partitioned well into the oil phase, exist in a somewhat "protected" environment in which the hydrogen-bonded conformation is relatively undisturbed. The more active, hydrophilic couplers are not only more accessible to developer, but also encounter competition from external hydrogen-bonding to the aqueous phase, disrupting the hindered conformation.

Conformational Effects

Steric effects in organic reactions are best studied by three-dimensional techniques. Using the SIMS[1] program, a data set containing drawings of thirteen pyrazolone couplers was created. A conformational energy minimization using molecular mechanics and molecular dynamics was performed on each coupler. The low energy conformations found for the couplers showed significant hydrogen bonding on the ballast fragment between the NH hydrogen of the amide functionality and the oxygen of the aryloxy ring. Figure 2 shows that this hydrogen-bonded conformation places the ballast in front of the coupling site where it can manifest its ability to sterically hinder the formation of leuco dye.

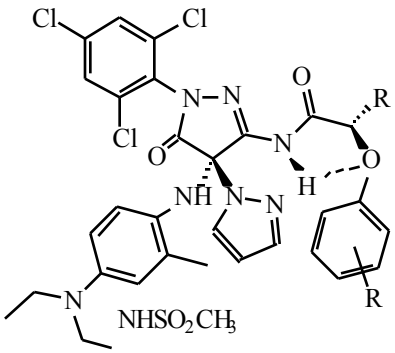

Figure 2. Tetrahedral leuco dye intermediate.

A rendering of a CPK model of the tetrahedral intermediate of 4 showed considerable crowding of the van der Waals surfaces of the ballast and the pyrazole coupling-off group. The additional phenyl ring in the ballast of 6 extends the steric components further from the coupling site. Consequently, there was a larger "pocket" for a more facile formation of the tetrahedral leuco intermediate and a resultant 50% increase in coupler activity. This is consistent with the conclusions made from studies on the hydrophobic effect. Hydrophobic couplers, partitioned well into the oil phase, exist in a somewhat "protected" environment in which the hydrogen-bonded conformation is relatively undisturbed. The more active, hydrophilic couplers are not only more accessible to developer, but also encounter competition from external hydrogen-bonding to the aqueous phase, disrupting the hindered conformation.

Molecular Modeling and QSAR Studies

The synthetic strategy provided a qualitative understanding of the structure/activity relationships of two-equivalent, pyrazolone magenta couplers. The SIMS and PLSPC[3] statistics programs were used to derive a quantitative structure/activity model. The goals of the modeling study were (1) to synthesize a small number of compounds, a "data set" that would allow the calculation of a suitable model, (2) to use the model to predict activities of future couplers, including those that do not strictly adhere to the data set's structural class and (3) to further understand the factors affecting the coupling reaction.

The 13 couplers that had been synthesized to explore solubility, steric, and conformational effects, encompassed a suitably broad range of structural variations and were thus used in this modeling study. The structures were drawn in the enolate form, the active form of the molecule during the coupling reaction under study. Molecular mechanics, an empirical energy model, was used to estimate the lowest energy conformations of the couplers.[4] To avoid converging on local energy minima, molecular dynamics were applied. Molecular dynamics simulations attempt to find a "global" energy minima by more extensively exploring conformational space before localizing on a particular low energy conformation. More specifically, a technique known as "quenched molecular dynamics" was applied to each of the structures. In this simulation, the molecule was heated to a very high temperature (in which high energy

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conformations are possible) and then cooled down slowly to a very low temperature. As the molecule lost kinetic energy it was no longer able to surmount large energy barriers but should have been able to escape shallow energy wells (local energy minima). In this way, the molecule eventually found its way to the deepest energy well, i.e., the "global" minima. When the lowest energy conformations were found, the pyrazolone fragment of the couplers, which was constant for all couplers, was deleted for ease of calculation. The NH of the amide was exchanged for OH to approximate only one hydrogen available for hydrogen bonding, essentially leaving the structure of the ballast carboxylic acids. For each of these compounds, a measured D-max for the corresponding coupler was entered into a table of dependent variables. The molecules were oriented along the same coordinates and theoretical physical and structural properties calculated. Table 1 shows a printout of the table of physical properties calculated for the coupler 4 ballast by SIMS. (For definitions of these parameters, see Appendix A). These properties, along with the Kier-Hall topological indices, were used as the independent variables to create a cross-validated mathematical model describing the structure/activity relationships. Unlike classical QSAR studies, this analysis was not limited to a series of ring substituents (e.g., a Hammett series) but instead, the entire ballast fragment was modeled. This was appropriate, based on previous qualitative observations regarding the importance of size and shape of the ballast to coupler activity. The statistical techniques used were also non-traditional in the sense that standard multiple linear regression and correlation analyses were not used, in favor of the partial least squares (PLS) method. This technique is not limited to using only a few "important" variables. It uses any, or all descriptor information selected, maximizing the fit, while minimizing overfitting. In classical QSAR studies, highly correlated parameters are not used within the same mathematical equation since it is redundant information. However, PLS makes use of redundant information, in a sense, decreasing the "noise" in the calculated parameter[5]. The model terms are linear combinations of the selected variables.

Table 1. Calculated physical properties of ballast 4.

FILE: Coupler 4 / ballast acid

FORMULA: $C_{30}H_{52}O_3$

Mass	460.74	Volume	502.29	SArea	572.84
Shape	-0.92	SABC	91.12	SAAC	120.73
SAAB	124.96	RA	3.13	RB	5.50
RC	5.74	MUA	-2.86	MUB	3.83
MUC	1.04	Dipole	4.85	Vloop1	3.34
Vloop2	6.45	Vloop3	8.40	Vloop4	9.15
Vloop5	11.03	ClogP	10.48	CMR	140.24
NHBD	1.00	NHBA	3.00	NHB	1.00
ETot	-16.88	EStr	0.43	EBend	2.56
ETors	4.65	EOOP	0.01	EvdW	24.52

The PLS modeling report, described the leveraging of the data set compounds in the creation of the mathematical model. The program identified two compounds as being heavily leveraged and suggested examining the points. The two compounds were originally synthesized to examine the effect of moving the sterically hindering group farther from the coupling site in compounds of high and low ClogP. Since these compounds contributed to the qualitative understanding of the structure/activity relationship, and since the compounds were leveraged only slightly higher than the recommended amount, a judgment was made to keep the compounds in the data set.

A cross validation summary was run on the model to ensure that it would be useful for predictive purposes and to select the optimum number of PLS dimensions in the model. The number of dimensions in a PLS model can be compared to the number of independent variables in a classical QSAR equation in the sense that an insufficient number of dimensions does not produce the best possible fit to the data. Too many dimensions will overfit the data and lead to poor predictions for compounds that deviate structurally from those in the data set. The cross validation summary indicated that the optimum dimensionality for this model was three, a suitable number for a data set of 13 compounds. The cross validated, 3-dimension PLS model for the magenta coupler data set is shown in the top half of Table 2. The observed versus predicted values are quite good with an R^2 of 0.94. This prompted using the model to predict activities for compounds not yet evaluated, as well as couplers synthesized by other chemists, following other synthetic strategies.

A new data set was created with the original 13 couplers plus 8 additional couplers (15 - 22). The new compounds were submitted to the same processes for conformational energy minimization and calculation of the physical and topological properties. The new data set did not include the dependent variable, D-max. The program was directed to predict values for D-max using the mathematical model created from the original thirteen compound data set. The program calculates "P" values for each compound, measuring the likelihood that it came from the original dataset. This is extremely valuable because it indicates when the predicted values are extrapolated and can serve as a guide as to the confidence one can have in the predicted value. The program readily identified the 13 original couplers. It also identified the values predicted for 21 and 22 as being borderline extrapolations. From the predicted versus observed values, it can be seen that the program did quite well in predicting D-max for the new compounds. As expected from the calculated "P" values, 21 and 22 were not as well predicted as the six other new compounds. This does not necessarily imply a poor model, but rather that these compounds were not well represented by this model. Examination of the structure of these compounds showed that they contained functional groups and ring substitution patterns atypical of those in the original data set. Nevertheless, the model was able to do well enough to predict "ballpark" activities. Adding 21 and 22 to the original data set to represent other couplers of this structural type would expand the utility of this model.

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Table 2. Cross validated 3-dimensional model.

DESCRIPTION OF THE INPUT DATA:
Number of Observations.....13
Number of Exogenous (X) Variables.....86
Number of Endogenous (Y) Variables.... 1
Number of Dimensions in the Model..... 3

ID	Pred.	Obs.	Residual
1	1.02	0.95	0.07
3	0.77	0.87	-0.10
4	0.79	0.81	-0.02
5	0.79	0.72	0.07
6	1.00	1.00	0.00
7	0.47	0.51	-0.04
8	0.91	0.86	0.05
9	1.22	1.24	-0.02
10	1.21	1.26	-0.05
11	0.52	0.55	-0.03
12	0.55	0.59	-0.04
13	0.89	0.90	-0.01
14	0.80	0.75	0.05
Prediction	*of D-max*		
15	0.61	0.61	0.00
16	1.03	1.04	0.01
17	1.04	0.96	0.08
18	1.10	1.19	0.09
19	0.98	1.09	0.11
20	0.70	0.82	0.12
21	0.69	0.85	0.16
22	0.82	1.10	0.28

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This modeling exercise was an attempt to apply computational tools to photographic chemistry. The tool is still in its infancy regarding this application, but continued work in this area could prove it to be an immensely valuable aid to the design chemist.

Hue Shifts

The couplers studied in this work formed image dyes with various lambda-max absorptions. The hue shifts could not be explained in terms of electronic or environmental (i.e., coupler solvent) factors. In studying the data for approximately 60 couplers structurally capable of forming the hydrogen bonded conformation described above, it was observed that they could be divided into 3 clusters: 544 nm, 548 nm, and 553 nm. Upon viewing the "3D" CPK structures, a trend was observed. Compounds with large, sterically hindering ballasts (as previously described) typically exhibited lambda max in the 553 nm range. Moderately hindered couplers absorbed in the 548 nm range and less sterically hindered couplers absorbed at 544 nm. This correlated with the effects these ballasts had on activity. If a ballast could hinder formation of the leuco dye due to van der Waals interaction, then it might also affect the bond angle of the dye formed. This would affect the pi overlap of the conjugated system and consequently the wavelength at which the dye absorbed.

Typical examples of this phenomenon are shown in Fig. 3. Coupler 4 absorbed at 548 nm. Introduction of a phenyl ring in 6 that moved the bulky groups away from the dye chromophore resulted in a 5nm hypsochromic shift. Coupler 20 with an ortho *tert*-octyl group absorbed at 548 nm. Moving this functionality to the para position also resulted in a 5 nm hypsochromic shift. This could only be explained in terms of steric interactions as the electronic and solubility properties of the two compounds were essentially equal. Comparison of the CPK structures of these compounds illustrated how the ortho substituent could affect the positioning of the phenylenediamine group. Coupler 4, with branched *tert*-pentyl groups underwent a 4 nm hypsochromic shift when substituted with flexible n-pentyl groups as in 8. A dramatic hypsochromic shift of 7 nm was observed when the ortho substituent of 27 was moved to the para position, further from the dye chromophore. Although quantitative measurements were not used to calculate dye absorption, the use of molecular modeling as a visualization tool enabled some mechanistic understanding of the observed shifts in dye hue.

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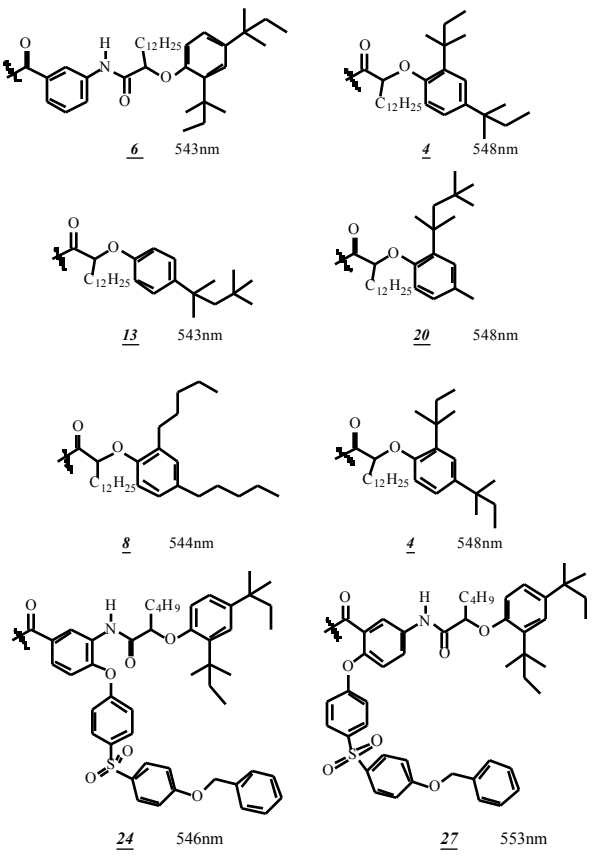

Figure 3. Ballasts affecting the hue of pyrazolone couplers.

Conclusion

The QSAR studies on two-equivalent pyrazolone magenta couplers provided mechanistic insight to the relationship between the stuctural and physical properties of these couplers and their photographic activity. This information allowed the design chemists to identify properties which could be manipulated to control activity and hue.

References

1. Richard Hildebrand, Structure Index Modeling System.
2. C. Hansch and A. Leo in *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley Interscience, New York, 1979.
3. Charles Heckler, PLSPC.
4. For a reference on this topic, see U. Burkert and N. L. Allinger in *ACS Monograph 177*, American Chemical Society, Washington, D. C. 1982
5. Charles Heckler, private communication.

Appendix A: Definitions of Calculated Properties*

Volume - The total volume of the CPK model for the molecule in which each atom is represented as a sphere with a radius corresponding to its van der Waals radius and calculated by numerical integration.

Sarea - The total surface area of the CPK model as described above for the volume calculation.

RA, RB, RC - The radii of gyration of the molecule, calculated for all atoms having unit weight. In the principal axis system, the radii of gyration are the root-mean-square distance of the atoms from each of the axis and are ordered with RA being the smallest and RC being the largest.

SHAPE - Shape is a function of the 3 radii of gyration:
Shape = $(2/r_b^2 - 1/r_a^2 - 1/r_c^2) / (1/r_a^2 - 1/r_c^2)$

SABC - The shadow area of the molecule in the AB principal plane is the area of the shadow which would be cast by a parallel light beam impinging along the C axis (the one with the largest radius of gyration). The other two shadow areas SAAC and SAAB have a corresponding interpretation.

MUA - The dipole moment along the A principal axis, m_a. *MUB* and *MUC* have a corresponding interpretation

Dipole - The total dipole moment, m, in Debye units is the magnitude of the vector with the three components MUA, *MUB*, and *MUC*.

Vloop - Also known as Sterimol parameters. Verloop1 is defined as the length of the substituent along the axis of the bond between the first atom of the substituent and the parent molecule fragment. Verloop 2, 3, 4, and 5, are the width parameters determined by the perpendicular distances from the axis to the outside of the van der Waals surface at 90 degree orientations.

ClogP - The estimated value for the logarithm of the octanol-water partition coefficient.

CMR - The estimated value for the molecular refractivity based on the same additivity formulation as used for ClogP but with different atomic coefficients.

NHBD - The number of hydrogen bond donors.

NHBA - The number of hydrogen bond acceptors.

NHB - The number of internal hydrogen bonds which are formed in the molecule.

ETOT - The total strain energy obtained in the molecular mechanics calculation.

EStr - The component of the total strain energy which comes from bond stretching, and/or compression.

Ebend - The component of total strain energy which comes from angle strain.

ETors - The torsional component of the total strain energy.

EOOP - The component of the strain energy which arises from out of plane bending of the planar four atom moieties.

EvdW - This is the non-bonded van der Waals contribution to the total strain energy.

* Reprinted in part from ***The SIMS Version 1.0 User's Manual*** written by Richard Hildebrandt.