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Recent studies on conformational analysis and steric effects

Jeffrey I. Seeman

Philip Morris Research Center, P. O. Box 26583, Richmond, Virginia 23261 USA

Abstract - Conformational analysis and steric effect models are used in four different applications. A new conformational analysis model for organotransition metal complexes of the type $(\eta^5\text{-}C_5H_5)M(Ph_3P)(L)R$ where M = Fe or Re and L = CO or NO is used to rationalize the structure and some stereospecific reactions that these complexes undergo. Two different steric models are presented which correlate the rate of N-alkylation of alkyl-substituted pyridines and quinolines as well as acyclic amines and cyclic nonaromatic amines using molecular mechanics/molecular orbital derived steric energies. The stereoselectivities of methylation of conformationally mobile nicotine analogs are examined with regard to steric and electronic effects. The Curtin-Hammett principle and the Winstein-Holness equation allow quantitative analysis of the kinetics.

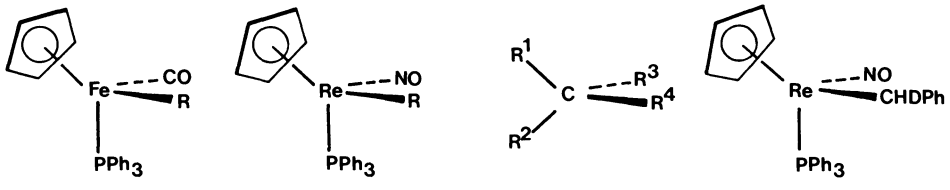
I. INTRODUCTION

Subtle structural and conformational characteristics can have major consequences on chemical properties. During the last few years, we have developed a variety of conformational analysis models and steric effect models. One goal has been to understand in a qualitative sense varied stereochemical features in emerging areas of chemistry. A second equally important goal has been to correlate chemical kinetics with steric, electronic, and conformational properties of molecules.

In the next Section, we present a new conformational analysis model for some octahedral organotransition metal complexes, which forms the basis for understanding a wide range of structural phenomena and stereospecific reactions. In Section III, we illustrate how one can quantify structural (geometric) variations which can significantly modify chemical reactivities. In Section IV, we examine steric and electronic effects in systems having multiple reacting conformations, each of which gives a different product.

II. MOLECULAR GEOMETRY AND ORGANOTRANSITION METAL CHEMISTRY

Organotransition metal complexes generalized by $(\eta^5\text{-}C_5H_5)Fe(Ph_3P)(CO)R$ (1) and $(\eta^5\text{-}C_5H_5)Re(Ph_3P)(NO)R$ (2) where R = alkyl, acyl, etc. are very versatile synthetic intermediates (ref. 1, 2). A wide variety of highly stereoselective reactions at the organic ligand R of 1 and 2 have been reported during the last decade (ref. 3,4). During this period, complexes of the type 1 and 2 were called "pseudotetrahedral" (ref. 5). By analogy to carbon compounds, structures 1-3 are superficially similar: four different groups are attached to a single atom, thereby leading to enantiomers and the possibility of optical resolution. In further analogy, diastereomers of 1-2 are possible and have been observed (e.g., 4, ref. 6) for complexes which possessed chiral atom(s) on the organic ligand, R.



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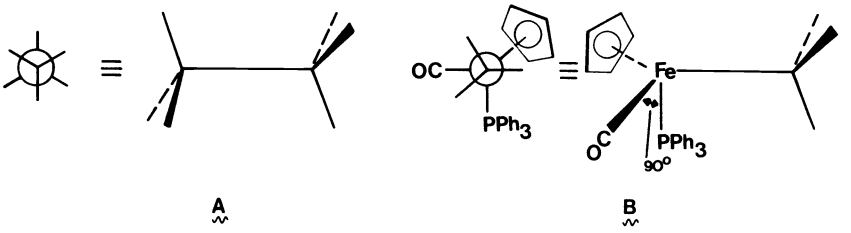


Figure 1. Comparison of a C_{sp3}-C_{sp3} molecule (A) with an organotransition metal complex (B). Note that in A, three perfectly staggered conformations are possible. In B, due to the unequal "bite" angles about the transition metal, neither perfectly staggered nor perfectly eclipsed conformations are possible. Also, in A, all three of the "back" atoms fall behind the plane which intersects the "back" carbon atom and is perpendicular to the C-C bond. In B, the P and carbon atom of the CO ligand form a plane with the iron which is perpendicular to the Fe-C_α bond axis; only the η^5-C_5H_5 ligand lies behind that plane.

In the early 1970's, Stanley, Baird, and coworkers proposed (ref. 7-12) what was at that time a pioneering conformational analysis model for $(\eta^5\text{-}C_5H_5)Fe(Ph_3P)(CO)R$ (R=alkyl) which was subsequently extended by others (c.f. below) to the rhenium analogues $(\eta^5\text{-}C_5H_5)Re(Ph_3P)(NO)R$. Using a tetrahedral geometry model in terms of Newman projections, they postulated that $(\eta^5\text{-}C_5H_5)Fe(Ph_3P)(CO)CH_2Ph$ (5) would exist in one of three possible staggered conformations, 5A, 5B, or 5C (Chart I). Proton NMR results indicated that one C_α-H was gauche to P and the other was anti to P; based on the reasonable assumption that CO was the smallest ligand, Stanley and Baird concluded that 5A was the most stable conformation (ref. 7-12). They further claimed "that the order of decreasing ligand steric requirements is η^5-C_5H_5 > L > CO" (L=Ph_3P) (ref. 11). This tetrahedral model was subsequently used by other investigators (ref. 6, 13-15) and appears frequently in the 1983 edition of the Gmelin Handbook featuring iron chemistry.

Seeman and Davies (S-D) have developed an alternative model for the conformational analysis of 1-2 and related complexes (Chart I, ref. 4,5,16). The S-D model is based on examination of an extensive set of X-ray crystallographic results and on extended Huckel (EH) calculations performed on a number of different series of iron and rhenium complexes. Complexes 1-2 are in fact nearly octahedral in character, where the bond angle between the cyclopentadienyl (Cp) ligand, the metal, and any of the other three ligands is ca. 125° and the bond angle between any two of the ligands {Ph_3P, CO/NO, and R} and the metal is ca. 90°. A comparison (ref. 17,18) of the tetrahedral (S-B) model and the octahedral (S-D) model is shown in Chart I and Figure 1. A series of conclusions can be made: first, contrary to the S-B model, the cyclopentadienyl ligand is not the controlling factor in terms of steric bulk, since it is bent back, away from the other three ligands; second, the CO/NO and PPh_3 ligands are bent forward in B relative to A; third, considering the Newman projections, the "bite" angles <Cp-M-P and <Cp-M-CO are considerably larger than the "bite" angle <P-M-CO = 90°; and fourth, these results imply that the Ph_3P ligand will be the most sterically demanding, and that the volume or space within the "bite" angle <P-M-CO will be the least favorable for any bulky substituent.

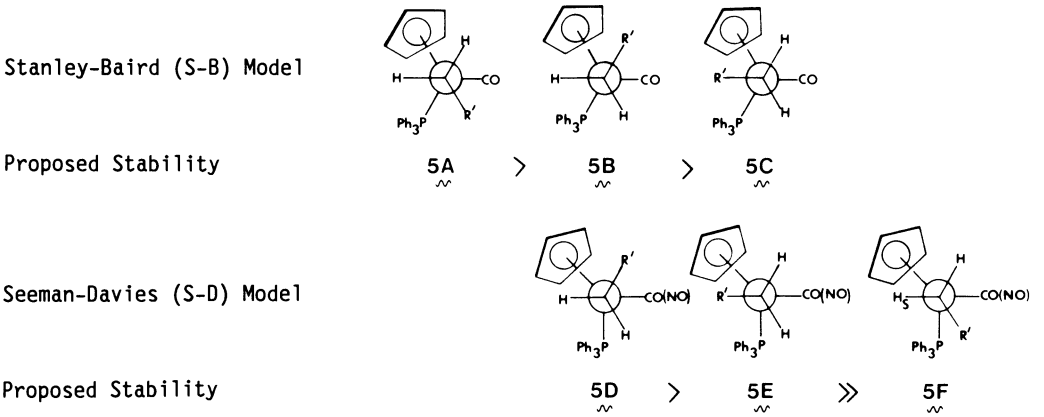


Chart I. Order of Stability of Conformations for the Two Models

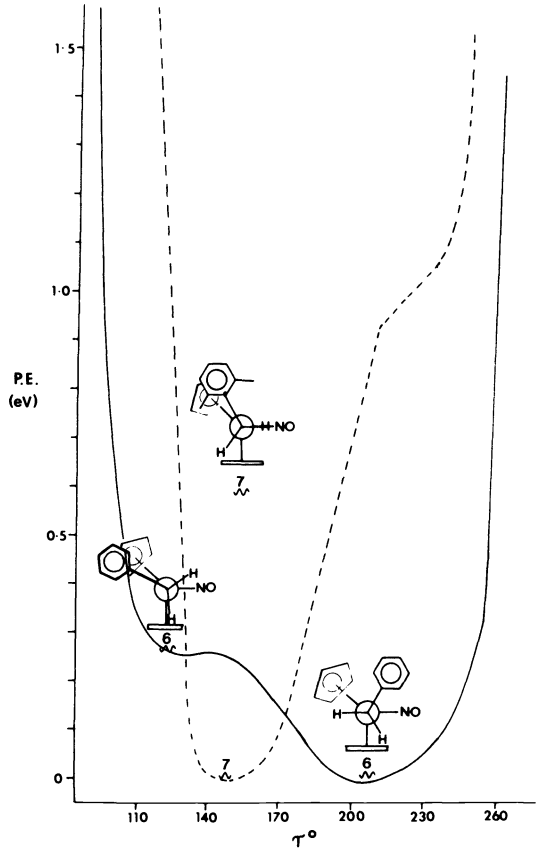
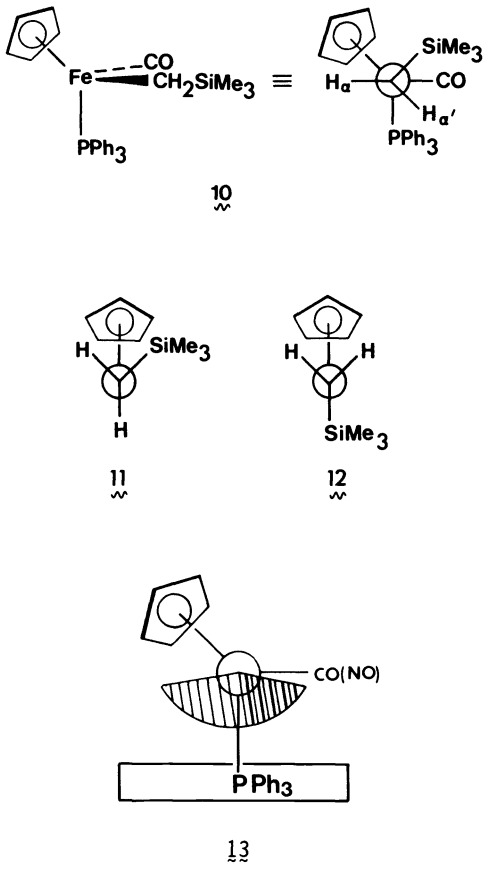


Figure 2. Calculated potential energy vs. torsional angle $\tau(C_{ipso}\text{-}C_\alpha\text{-}Fe\text{-}P)$ for: $(\eta^5\text{-}C_5H_5)Re(NO)(PPhH_2)CH_2Ph$ (6) (solid line) and $(\eta^5\text{-}C_5H_5)Re(NO)(PPhH_2)C_\alpha H_2(2,6\text{-}C_6H_3Me_2)$ (7).

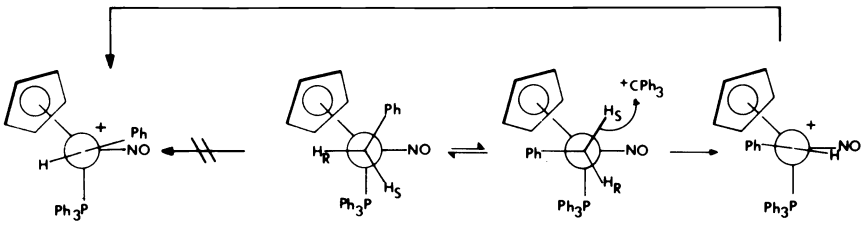


For calculational purposes in this field, it has been standard practice to use the PH_3-substituted analogs as models, e.g., $(\eta^5\text{-}C_5H_5)Re(PH_3)(NO)R$ (ref. 19-20). For more accurately defining the nature of the torsional energy minima, we have found that inclusion of one P-phenyl ring, positioned below the organic ligand R as found in numerous x-ray results for these complexes, is essential. Figure 2 displays the extended Huckel calculated potential energy curves for rotation about the Fe-C_α axis for $(\eta^5\text{-}C_5H_5)Re(PPhH_2)(NO)C_\alpha H_2Ph$ (6) and $(\eta^5\text{-}C_5H_5)Re(PPhH_2)(NO)CH_2(2,6\text{-}C_6H_3Me_2)$ (7) serving as models for $(\eta^5\text{-}C_5H_5)Re(PPh_3)(NO)CH_2Ph$ (8) and $(\eta^5\text{-}C_5H_5)Re(PPh_3)(NO)CH_2(2,6\text{-}C_6H_3Me_2)$ (9), respectively. The very steep rise in energy when $\tau < 110°$ and $\tau > 230°$ indicates that moving the $FeCH_2$-phenyl ring below the C_α-Re-NO plane results in considerable steric destabilization. Only a very narrow range of conformations is energetically available. The calculations excellently match the X-ray crystallographic data for $(\eta^5\text{-}C_5H_5)Re(Ph_3P)(NO)CH_2Ph$ excellently (ref. 21): (a) via EH, the plane of the C_α-phenyl group is essentially perpendicular to the plane containing C_{ipso}, C_α, and Re; experiment, $\tau = 84.5°$; (b) via EH, τ (P-Re-C_α-C_{ipso}) = 205°, experimental = 203°. Recently, Hunter and Baird reported (ref. 22) the results of NOE difference spectroscopy on $(\eta^5\text{-}C_5H_5)Fe(Ph_3P)(CO)CH_2SiMe_3$ (10) where irradiation of the cyclopentadienyl protons led to a positive NOE for one C_α-H and a negative NOE for the other C_α-H. This requires a partial structure of 11 rather than 12, consistent with the most stable conformation of the S-D model (Chart I).

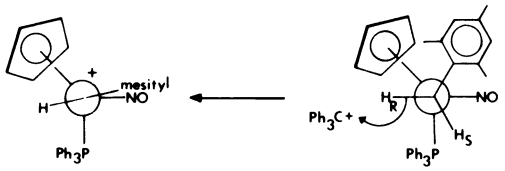
Structural and stereochemical results in this field appear to be consistent (a) with minimizing (or excluding) substituents on the alkyl ligand from taking positions much below the plane defined by C_α-Metal-CO(NO), the area within the P-Metal-CO(NO) bite angle being the least available (c.f. 13); and (b) with electrophiles or nucleophiles reacting with 1 and 2 in an direction anti to the PPh_3 group. These generalizations are shown by structure 13. To do otherwise results in significant molecular distortion and increases in strain and steric energy.

The S-D model (Chart I and 13) forms the basis for the evaluation of much of the stereochemical results for 1-2. Gladysz has reported many stereochemical results for 8 and 9 and

related complexes (ref. 6,19,21,23). Thus, treatment of 8 with trityl cation leads exclusively (eq 1) to the less stable Re=C product isomer 14 which then subsequently rearranges to the more stable isomer ac-(η^5-C_5H_5) Re(PPh_3)(NO)(=CHPh)$^+$ (15). Careful isotope studies proved that only H_S is abstracted (ref. 23). As seen in Figure 2, 6 and by extension 8 exist in two stable conformations. Because of the bulkiness of Ph_3C^+, this reagent prefers to attack both anti to the Ph_3P ligand and distant from the Cp ligand, since some of the carbons of the latter ligand can extend toward the plane containing Re, P, and NO. Reaction of the more substituted rhenium complex 9 with trityl cation (eq 2, ref. 6) must take place from the only conformation available to 9 (Figure 2) to give directly the more stable carbene 16. In this case, the extremely bulky mesityl group remains within the Cp-Re-NO bite angle (c.f. 13) while the electrophile abstracts the only available hydride H_R. The previous model or extensions thereof for this and related chemistry did not allow interpretation of the stereochemical results (ref. 6,13,23).

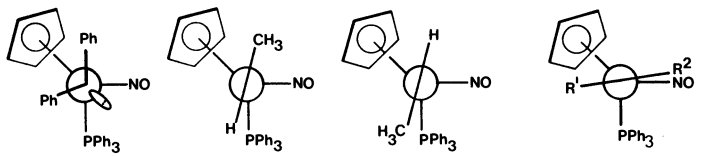


15 8 14 (1)



16 9 (2)

Gladysz et al. recently reported the synthesis and X-ray crystallographic structural analysis of the rhenium phosphide complex (η^5-C_5H_5)Re(Ph_3P)(NO)PPh_2 (17) (ref. 19). In the crystal, the molecule adopts the conformation as indicated. A stereoelectronic phenomenon was advanced as a contributing factor to explain this conformation, namely a "gauche effect" in transition metal chemistry: the lone pair of the ligating atom is orthogonal to the HOMO of the metal fragment. A steric effect may play the dominant role (c.f. 13), as neither of the P_α-phenyl groups of the Ph_2P ligand can reside within the Ph_3P-Re-NO bite angle. The EH calculations reported to support this "gauche effect" were performed on the model compound (η^5-C_5H_5)Re(PH_3)(NO)PH_2, an analogue unlikely to exhibit the steric hindrance which dominates the (η^5-C_5H_5)Re(Ph_3P)(NO)PPh_2 conformational energy profile.



17 18 19 20a, R^1=H, R^2=CH_3; b, R^1=CH_3, R^2=H

To comment on the influence of simultaneously operating steric and stereoelectronic factors, we consider the conformational properties of the isomeric rhenium vinylidenes (η^5-C_5H_5)Re(Ph_3P)(NO)(=C=CHMe)$^+$ (20) for which an equilibrium constant K = 1 for the two stereoisomers was determined by ^{1}H NMR experiments (ref. 24). Gladysz and Wong suggested that these two isomers are 18 and 19. For 19, our model is seemingly contradicted because one alkyl substituent is pointing toward the Ph_3P ligand! Figure 3 illustrates our EH calculations for these molecules (ref. 25). If one allows the angle <P-Re-C_α to distort significantly (from 90° to 102°), a second minimum as predicted by Gladysz does appear. Alternatively, structures, 20a and/or 20b may obtain if conformations in which other molecular distortions (e.g., P-phenyl ring tilt) not modeled by our EH calculations (Figure 3) are important stabilizing features. Clearly, additional experimental data is necessary to elucidate which molecular distortions are most crucial in simultaneously relieving steric strain and allowing for stereoelectronic stabilizations. We await X-ray crystallographic analysis of substituted vinylidines to distinguish between these alternatives.

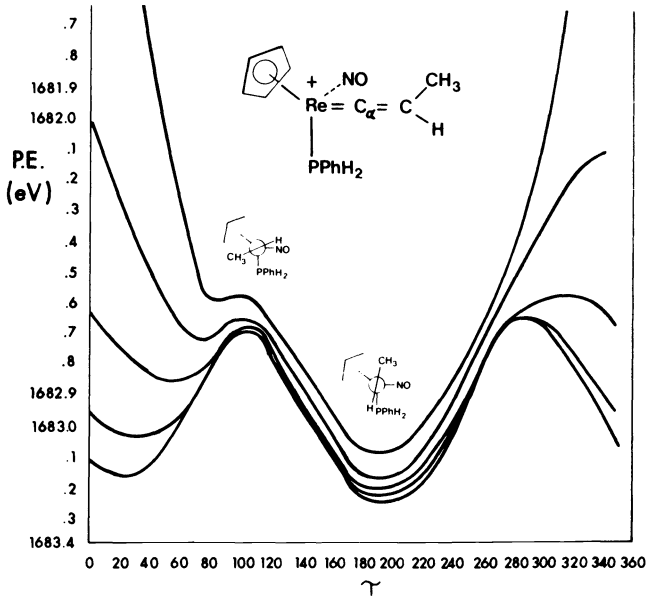
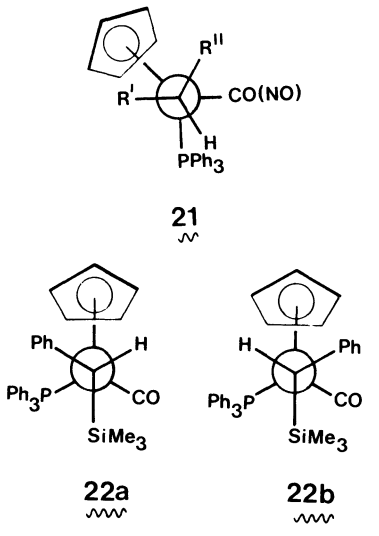


Figure 3. Calculated potential energy vs. τ(P-Re-C_α-C_β) for $(\eta^5\text{-}C_5H_5)Re(PhPH_2)(NO)(=C=CHMe)^+$.



The S-D model predicts that complexes of the type $(\eta^5\text{-}C_5H_5)M(Ph_3P)(CO/NO)CHR^1R^2$ will have 21 as their most stable conformation. In contrast, Stanley and Baird concluded that the most stable conformations of the diastereomers of $(\eta^5\text{-}C_5H_5)Fe(Ph_3P)(CO)CHPhSiMe_3$ were 22a and 22b respectively, in which the "bulky $\eta^5\text{-}C_5H_5$ and $SiMe_3$ groups are mutually trans" (ref 11). EH calculations (ref. 4) and Gladysz' X-ray structure for $(\eta^5\text{-}C_5H_5)Re(Ph_3P)(NO)\text{-}CH(CH_2Ph)Ph$ (ref. 13) are consistent only with 21 (and 13).

In this Section, we have illustrated the latest conformational analysis model for understanding and interpreting the chemistry of complexes 1 and 2. Future areas of attention will include (a) new procedures for the synthesis of asymmetric compounds; (b) structures and conformational analysis of complexes having nonadditive substituent effects (c.f. Section III); and (c) evaluation of transition state energetics and interactions. The S-D model can serve as the framework from which more mature models will be built and as a stimulus for hypothesis-testing.

III. QUANTIFICATION OF STERIC EFFECTS

Most of the successful quantification of chemical reactivity to date has been based on linear free energy relationships (LFER) (ref. 26-28). This approach assumes additivity of substituent effects and has notably failed to model successfully steric effects because these are typically nonadditive and non-transferable from one reaction-type or substrate-type to another (ref. 29-34). Nonadditive substituent effects on kinetics implies nonadditive structural variations during the course of the chemical transformation.

The Menschutkin reaction of pyridines with various alkylating agents is well known to be controlled by both steric and electronic effects. A simple procedure to quantify nonadditive kinetic and structural effects was sought. Alkyl groups have approximately the same electronic effect on the Menschutkin reaction (a rate acceleration of ca. 2.2 per alkyl group), independent of position (ref. 30,35). To quantify relationships between ground state geometry and reaction kinetics, we examined the methylation of a series of pyridines having essentially a constant "substituent" at C_2, whose position relative to the nitrogen atom varied due to the presence of other substituents (c.f. Table I and 23). Molecular geometry estimates were based on MINDO/3 calculations, which are known to accurately reproduce heteroaromatic structures. Kinetic nonadditivity was quantified by the parameter $S = k_{obs}/k_{calc}$ where k_{calc} was derived using LFER [i.e., $k_{calc} = \pi\, k_{(rel)i}$, where $k_{(rel)i}$ are the relative rate constants for methylation of the monosubstituted pyridines].

As illustrated by eq 3 and Figure 4, an excellent correlation is obtained for the methylation of the compounds listed in Table I (ref. 30,35). Table I also shows that θ (c.f. 23) varies substantially, from a minimum of ca. 110° for 2-methyl-3-t-butylpyridine, as calculated by the MINDO/3 algorithm, to ca. 127° for 2,3-cyclopentenopyridine. 2,3-Cyclopentenopyridine methylates nearly six times faster than 2-methyl-3-t-butylpyridine.

Table I. Steric Accessibility Factors and Geometric Parameters[a] for Methylation of 2-Substituted Pyridines

Compound	k_{rel}	S[b]	θ[a,c]
pyridine	1.0	1.0	-
2-picoline	0.43	1.0	117.0
2,3-lutidine	0.43	0.59	114.2
2,4-lutidine	0.92	1.0	117.1
2,5-lutidine	0.82	1.1	117.4
2-methyl-3-ethylpyridine	0.48	0.51	113.6
2-methyl-5-ethylpyridine	1.1	1.2	117.5
2-methyl-3-isopropylpyridine	0.51	0.49	113.2
2-methyl-5-isopropylpyridine	1.2	1.2	117.5
2-methyl-3-tert-butylpyridine	0.33	0.27	110.3
2-methyl-5-tert-butylpyridine	1.3	1.1	117.6
2,3-cyclopentenopyridine	1.9	2.6	127.1
2,3-cyclohexenopyridine	1.1	1.5	117.4
2,3-cycloheptenopyridine	0.3	0.41	114.1

a Geometries obtained via complete MINDO/3 energy minimization calculations. b $S = k_{rel}/k_{calcd}$; k_{calcd} was derived using LFER. The deviation of S from unity is a measure of kinetic nonadditivity. c N-C_2-$C_{2\alpha}$ angle.

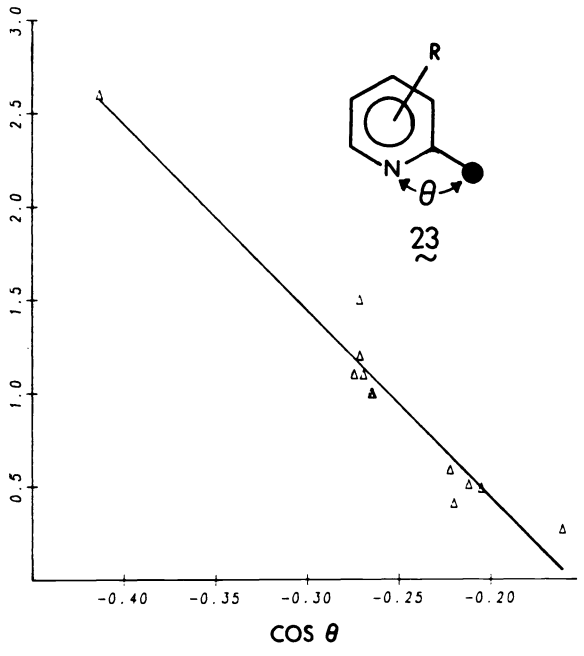


Figure 4. Relationship between S and θ for 2-substituted pyridines (c.f. eq 3).

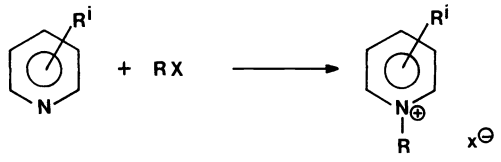
This is an amazing rate ratio considering the more reactive of the two is nearly 1 pka unit less basic and keeping in mind that pyridine itself methylates only about twice as fast as 2-picoline. Equation 3 is important because it mathematically relates structural features, i.e., the position of the α-substituent, with nonadditive kinetics.

$$S = -10.0 \cos \theta - 1.56 \quad (3)$$

[r = 0.964, n = 13, std. dev. of residuals = 0.0165]

While other ground state and transition state models for pyridine alkylations are available (ref 30, 36-40), our latest model was developed to fulfill the following criteria: (1) to be simple; (2) to reflect transition state and product geometry; (3) to handle a variety of alkylating agents; (4) to treat electronic effects; (5) to apply to other systems, e.g., acyclic amines; and (6) to be based on molecular mechanics (MM) rather than semi-empirical algorithms.

As the required empirical force fields for alkyl-substituted pyridines and N-alkylpyridinium cations are not available, the homomorphic transformation shown in eq 4 was employed as a model for the generalized Menschutkin reaction (eq 5) (ref 41). Steric hindrance will retard the Menschutkin reaction as R and R' (a) increase in size; (b) assume vicinal or buttressing positions; and (c) increase in number. This is reflected by an increase in net steric energy ΔSE, as shown in eq 6 (ref. 42-45).



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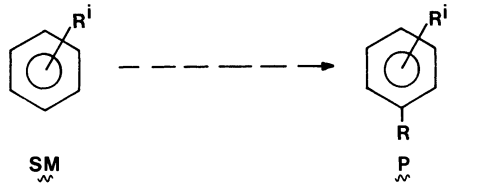


(5)

where R = CH_3, CH_3CH_2, $(CH_3)_2CH$; and R^i = H or alkyl, i = 0-5 (0-5 substituents).

$$\Delta SE = SE(P) - SE(SM) \quad (6)$$

where SE = MM calculated steric energies of substrates in eq 5.

To account for the rate enhancing electronic effects of the alkyl substituents, Gallo's adaption (ref. 46) of the Brønsted relation was utilized. Thus, for the methylation of pyridines unsubstituted at either C_2 or C_6, an excellent Brønsted line (eq 7) can be found to correlate alkylation rate with basicity. Gallo et al. (ref. 46) recognized that, for pyridines subjected to steric effects, the difference between the actual alkylation rate constant and that predicted purely on the basis of pKa will be a measure of steric effects. A new steric effect parameter S^o was derived (eq 8) based on the experimental determination of alkylation rate constants and pKa's.

$$\log \underline{k} = \alpha \text{ pKa} + c \tag{7}$$

$$S^o = \log \underline{k} - (\alpha \text{ pKa} + c) \tag{8}$$

Ultimately, one desires a relationship which predicts the value of the rate constant $\underline{k}$ for eq 5 chemistry. Our MM-based model was designed to provide a measure of the net steric consequences (i.e., ΔSE, eq 6) of the alkylation reaction. Hence,

$$\log \underline{k} = c_1 \Delta SE + c_2 \text{ pKa} + c_3 \tag{9}$$

The relevant experimental and theoretical data are listed in Table II for 56 alkylations. An excellent correlation is found (eq 10) when log $\underline{k}$ is treated as a dependent variable and ΔSE and pKa as independent variables. Improved correlations are obtained if we separate the fifty six alkylations into two groups, those having a single Cα-substituent (n = 44) (eq 11) and those with two C_α-substituents (n = 12) (eq 12).

$$\log \underline{k}_{All} = -0.86 \Delta SE + 0.34 \text{ pKa} - 5.5 \tag{10}$$

(n=56, r=0.94,f value for ΔSE=373.7,f value for pKa=13.6,std. dev. of res.=0.57)

$$\log \underline{k}_{mono} = -0.80 \Delta SE + 0.70 \text{ pKa} - 7.5 \tag{11}$$

(n=44, r=0.96,f value for ΔSE=379.1,f value for pKa=50.9,std.dev. of res.=0.35)

$$\log \underline{k}_{di} = -0.89 \Delta SE + 0.35 \text{ pKa} - 5.8 \tag{12}$$

(n=12,r=0.97,f value for ΔSE=61.5,f value for pKa=7.8,std.dev. of res.=0.41)

Table II. Methylation, Ethylation, and Isopropylation of Pyridines and Quinolines[a].

compound[a]	pKa[b]	ΔSE[e]	log k[d]	compound[a]	pKa	ΔSE[e]	log k
			methylations				
pyridine	5.19	-0.28	-3.50	cyclohepteno-	6.48	1.14	-4.02
2-M	5.97	0.24	-3.87	2-M,5-B	6.60	0.23	-3.39
2-E	5.89	0.45	-4.16	2-i-butyl	5.97	0.55	-4.46
2-P	5.83	0.88	-4.62	2-phenyl	4.48	0.75	-5.09
2-B	5.76	5.29	-7.16	2-benzyl	4.77	0.26	-4.41
2,3-M	6.75	1.37	-4.89	2-vinyl	4.98	0.29	-4.75
2-E,6-M	6.67	1.73	-5.95	2,5-M	6.42	0.28	-3.59
2,6-E	6.59	2.48	-5.93	2,3,5-M	6.79	0.90	-3.69
2-P,3-M	6.36	4.10	-6.01	2,3,6-M	7.16	2.02	-5.09
2,6-P	6.47	3.55	-7.32	2,3,4,6-M	8.05	2.02	-5.01
2,3-M	6.56	0.89	-3.87	2,4-M	6.72	0.25	-3.54
2,4,6-M	7.59	1.38	-4.46	3-M	5.63	-0.24	-3.27
2,3,5,6-M	7.90	2.17	-5.39	3-E	5.60	-0.26	-3.16
2,3,4,5,6-M	8.46	2.67	-5.32	3-P	5.72	-0.26	-3.12
2-M,3-E	6.59	1.02	-3.82	3-B	5.82	-0.28	-3.05
2-M,5-E	6.45	0.73	-3.46	4-M	6.05	-0.27	-3.18
2-M,3-P	6.63	1.33	-3.79	4-E	5.95	-0.27	-3.14
2-M,5-P	6.50	0.68	-3.42	4-P	6.02	-0.29	-3.16
2-M-3-B	6.81	1.37	-3.98	4-B	5.99	-0.32	-3.16
2-E,3-M	6.39	1.02	-4.12	quinoline	4.81	0.03	-4.46
2-E,5-M	6.39	0.48	-3.77	8-M Q	4.75	4.20	-7.62
2-P,5-M	6.32	0.92	-4.27	2-M Q	5.60	1.25	-5.71
cyclopenteno-	5.95	-0.51	-3.22	2,8-M Q	4.11	5.78	-9.47
cyclohexeno-	6.65	0.51	-3.46				
			ethylations				isopropylations
pyridine	5.19	0.69	-4.74	pyridine	5.19	2.03	-6.03
2-M	5.97	1.42	-5.37	2-M	5.97	3.19	-7.29
2-E	5.89	1.67	-5.71	2,6-M	6.75	7.53	-8.93
2-P	5.83	2.21	-6.26				
2,6-M	6.75	2.68	-7.11				
2,6-E	6.59	3.31	-8.19				

a M=Methyl, E=Ethyl, P=i-propyl, B=t-butyl, Q=quinoline. b Data from D. D. Perrin, Dissociation Constants of Organic Bases in Aqueous Solution, Butterworths, London (1965). c See equation 6. Calculated using Kao's MOMM-85 algorithm. See: J. Kao, D. Leister, and M. Sito, Tetrahedron Lett. 2403-2406 (1985). d From reference 30. e kcal mol^{-1}.

Table III. Alkylation of Acyclic and Cyclic Nonaromatic Amines.

compound	log k[a]	pKa[b]	ΔSE[c]
ethylations			
Me_3N	-2.19	9.75	3.08
Et_3N	-3.76	10.7	5.80
Pr_3N	-4.33	10.3	5.56
Bu_3N	-4.25	9.93	5.61
Et_2NH	-3.32	11.0	4.81
Pr_2NH	-3.46	11.0	4.79
Bu_2NH	-3.45	11.3	4.73
Et_2NCH_2CN	-6.13	4.55	4.96
$Et_2NCH_2CH_2CN$	-5.13	7.65	5.78
$HN(CH_2CN)_2$	-6.64	0.2	3.47
$HN(CH_2CH_2CN)_2$	-5.16	5.26	4.81
$PhNMe_2$	-5.26	5.10	4.52
$PhNEt_2$	-6.74	6.60	7.80
quinuclidine	-1.31	11.0	2.61
methylations			
quinuclidine	0.27	11.0	-0.02
Et_3N	-1.48	10.7	2.97
isopropylations			
Et_3N	-5.95	10.7	11.8
quinuclidine	-3.10	11.0	5.59

a Alkylation rate data from: W. A. Henderson, Jr. and C. J. Schultz J. Org. Chem. 27, 4643-4646 (1962); H. C. Brown and N. R. Elred, J. Am. Chem. Soc. 71, 445-450 (1949). b Data from D. D. Perrin, Dissociation Constants of Organic Bases in Aqueous Solution, Butterworths, London (1965). c See footnote c, Table II.

To explore the scope of this modeling procedure, we applied it to a series of acyclic and cyclic amines (Table III) having a pKa range of eleven orders of magnitude and a rate constant range of greater than seven orders of magnitude. Included in this series are both tertiary and secondary amines. In a fashion directly analogous to the heteroaromatic examples, eq 13 and eq 14 illustrate the chemical and the homomorphic reactions, respectively.

$$R^1R^2R^3N + R^4X \longrightarrow R^1R^2R^3R^4N^+ \ X^- \qquad (13)$$

$$R^1R^2R^3CH \longrightarrow R^1R^2R^3R^4C \qquad (14)$$

An excellent multiple correlation is obtained (eq 15), indicating the power of this modeling procedure.

$$\log k = -0.56\ \Delta SE + 0.43\ pKa - 5.0 \qquad (15)$$

(n=18,r=0.97, f value for ΔSE=124.3,f value for pK_a=120.4, std.dev. of res.=0.50)

The validity of any quantitative model is judged by the range of values accurately correlated. The alkylations cover rate ranges of 10^5 for nitrogen aromatic heterocycles and 10^7 for acyclic and nonaromatic cyclic compounds. The models presented herein can predict alkylation reactivities and also allow evaluation of nonadditive structural and substitutent effects. Particularly illustrative of the latter point is the correlation between the alkylation rate of 2-substituted pyridines and the "location" of the 2-substituent relative to the ring geometry.

IV. STERIC AND ELECTRONIC EFFECTS IN CONFORMATIONALLY MOBILE SYSTEMS

Organic compounds typically do not react via a single conformation, and frequently, more than one reaction product is possible. A kinetic system which models this complexity is that of Scheme I, where a molecule exists in two conformations, A_2 and A_3, each of which reacts to give a different product, A_1 and A_4 respectively. This is the Curtin-Hammett-/Winstein-Holness/Eliel-Ro kinetic system (ref. 47-48). The Curtin-Hammett (C-H) (eq 16) and the Winstein-Holness (W-H) equation (eq 17), when combined, lead to expressions for k_{21} and k_{34} as a function of three experimentally determinable parameters of Scheme I, K, $P = [A_4]/[A_1]$, and k_{W-H} (eq 18-19).

Table IV. Experimental and Calculated Parameters for the Methylation of 1-Methyl-2-(2- alkylphenyl)pyrrolidines (Scheme II).[a]

compound	k_{W-H}[b] (rel)	p[c]	K	k_{cis}[d] (rel)	k_{trans}[d] (rel)
24a	24	1.7	≥15	71	5.0
24b	6.1	1.4	>30	16	2.5
24c	4.9	1.3	>30	13	2.0
24d	4.2	1.3	>30	11	1.7
24e	1	0.38	>40	1	1

a Reference 49. b Total empirical reaction rate constant to products. c Product ratio. d Calculated using data in columns 1-3 of this table and eq 16-19.

Scheme I

$$A_1 \xleftarrow{k_{21}} A_2 \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} A_3 \xrightarrow{k_{34}} A_4$$

(For C-H/W-H kinetics to apply, $k_{23}, k_{32} >> k_{21}, k_{34}$.)

$$\frac{[A_4]}{[A_1]} = K \frac{k_{34}}{k_{21}} \tag{16}$$

$$k_{W-H} \equiv \chi_2 k_{21} + \chi_3 k_{34} \tag{17}$$

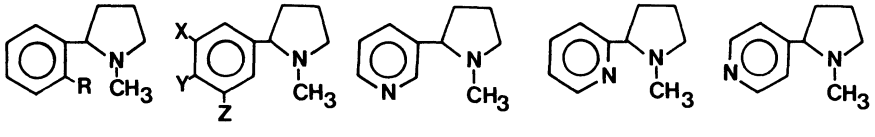
where χ_i = mole fraction of the i^{th} reactive conformation.

$$k_{21} = k_{W-H}[(K+1)/(P+1)] \tag{18}$$

$$k_{34} = k_{W-H}[(K+1)K]/[P/(P+1)] \tag{19}$$

where $P \equiv [A_4]/[A_1]$ and $k_{23}, k_{32} >> k_{21}, k_{34}$ for C-H/W-H kinetics to apply.

The methylation of a series of nicotine analogues 1-methyl-2-(2-alkylphenyl)pyrrolidines 24 (ref. 49) and 1-methyl-2-(3X,4Y,5Z-phenyl)pyrrolidines 25 (ref. 50) was studied to quantify cross-ring steric and electronic interactions in these nicotine (26) analogues. Scheme II illustrates the chemistry involved. As the rates of nitrogen inversion are known to be many orders of magnitude greater than the rates of nitrogen alkylation (ref. 51), these systems are accurately described by C-H/W-H kinetics (i.e, by eq 16-19).



24 25 26 27 28

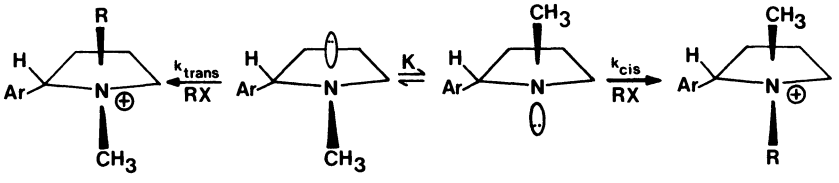
a, R = H
b, R = Me
c, R = Et
d, R = i-Pr
e, R = t-Bu

X,Y,Z = H, alkyl, halogen, OR, etc.

Table V. ^{1}H NMR Chemical Shifts for a Set of 1-Methyl-2-Arylpyrrolidines in CD_3CN.

proton	Chemical shifts(ppm) (ref. 50)						
	nicotine	27	28	25 X=Y=Z=OCH$_3$	25 X=Y=Z=H	25 X=Z=H,Y=F	Mean ± std dev.
2'	3.103	3.260	3.100	2.981	3.033	3.182	3.110 ± 0.100
3'α	1.659	1.710	1.600	1.634	1.642	1.641	1.648 ± 0.036
3'β	2.198	2.222	2.212	2.128	2.155	2.224	2.190 ± 0.039
4'α	1.901	1.842	1.836	1.864	1.879	1.914	1.873 ± 0.031
4'β	1.795	1.796	1.787	1.753	1.770	1.811	1.785 ± 0.021
5'α	3.172	3.162	3.171	3.147	3.158	3.201	3.169 ± 0.018
5'β	2.276	2.308	2.291	2.229	2.242	2.310	2.276 ± 0.034
N-CH$_3$	2.438	2.436	2.401	2.427	2.421	2.425	2.425 ± 0.013

Scheme II



To solve for k_{trans} and k_{cis} in Schemes I and II, three parameters, K, P, and k_{W-H} were experimentally determined.[21,34] Table IV summaries the experimental data for the methylation ($^{13}CH_3I$) of 24a-24e. The spread in values in k_{cis}(a factor of 71) is very impressive given the degree of flexibility within the molecule and the possibility of conformations in which the two rings are oriented such that the aryl-alkyl substituent could be anti to the N-methylpyrrolidinyl ring. Note that the ratio of methylation rate constants $k_{cis}(24a)/k_{cis}(24b)$ = 4.4 while the analogous ratio $k_{pyridine}/k_{2\text{-methylpyridine}}$ = 2.3 is smaller. In the latter system, the methyl substitutent is directly adjacent to the reactive nitrogen yet has a smaller net effect! Also of note is the apparent constancy in the product ratio P ≈ 1 while k_{W-H} and the individual reaction rate constants decisively and monotonically vary. P hovers around unity due to a balancing of effects. The already bonded N'-methyl group has nearly the same effective size that the N'----CH_3----I group has at the respective transition states, solvent effects being included implicitly. However, steric destabilizations slow down the entire reaction progress.

To evaluate electronic factors in nicotine analog chemistry, it was first necessary to establish that modification of the aromatic ring's electronic character would not alter the methylpyrrolidine's N'-methyl equilibrium distribution, K. The chemical shifts of all of the pyrrolidine protons for a subset of this series is shown in Table V. The pyrrolidine protons adjacent to the nitrogen atom are extremely sensitive to being either predominantly syn or anti to the lone pair of electrons of the nitrogen (ref. 51,52). For nicotine, K = ca. 15, the major conformation being that in which the N'-methyl group is anti to the pyridine ring. The ^{1}H resonance of $H_{5'\alpha}$, the proton syn to the nitrogen lone pair, is at δ 3.172, nearly one ppm downfield from $H_{5'\beta}$ at δ 2.276. If the value of K were to change within the series 25-28, this would be reflected in a change in the values of the $H_{5'}$ chemical shifts. As can be seen from Table V, the $H_{5'}$ chemical shifts remain constant throughout the series. Therefore, K is constant throughout this series.

Table VI lists the relevant experimental data and calculated values for k_{trans} and k_{cis} for nicotine and three of its analogues. While nicotine and 4-isonicotine 28 methylate at both nitrogen atoms (N'/N = 2.6 and 1.5 respectively), 2-isonicotine 27 methylates only at the N'-methyl group. This is consistent with decreasing the rate of N-methylation due to a bulky C-2 substituent. Considering only the nicotines 26-28, the pKa range is only ca. one pKa unit while $k_{N'}$ and k_{cis} vary by over a factor of ten. The only similar experimental data for alicyclic nitrogen alkylation is that of Grob and Schlageter (ref. 53), who studied a series of 4-substituted quinuclidines. Quinuclidine itself methylated only 6.7 times faster than 4-nitroquinuclidine, though it is 3.3 pKa units more basic. Furthermore, for these nicotinoids, the parent 1-methyl-2-phenylpyrrolidine is more basic than 2-isonicotine (pKa 9.27 vs 8.62) but it alkylates more slowly! These nicotinoids are very sensitive to electronic effects. The stereochemistry of methylation and the rate phenomena can be attributed to dipole-dipole interactions in the respective transition states. More details regarding the electronic properties of these molecules and the relevant transition states await the results of calculations being performed at present.

Table VI. Parameters for Methylation of 1-Methyl-2-arylpyrrolidines.[a]

compound	P[b]	k_{obs}[c] ($x10^3$)	N'/N[d]	k_N[e] ($x10^4$)	$k_{N'}$[e] ($x10^4$)	k_{cis}[f] ($x10^4$)	k_{trans}[f] ($x10^3$)
2-isonicotine (27)	2.0	9.8	>100	-	100.0	71.0	53.0
nicotine (26)	1.5	2.3	2.6	6.4	17.0	11.0	11.0
4-isonicotine (28)	1.1	1.6	1.5	7.6	8.4	4.7	6.4
1-methyl-2-phenyl-pyrrolidine	1.7	3.0	-	-	30.0	20.0	17.0

a From ref. 50. b Pyrrolidine alkylation product ratio $[A_4]/[A_1]$. c Total empirical reaction rate constant to all products. d Ratio of total N' (pyrrolidine) alkylation to N (pyridine) alkylation. e Total pyridine (N) and pyrrolidine (N') alkylation rate constants. e Calculated reaction rate constants, using eq 16-19 and K = 15.

In Section III, we modeled the reactivity of substituted pyridines and of various acyclic amines toward alkyl halides. One of the underlying assumptions of that modeling was the treatment of the reactants and reagents as if they were conformationally homogeneous. In this Section, we have quantitatively analyzed the reactivity of systems for which a minimum of two reactive conformations must be considered. The C-H and W-H concepts provide the mathematical basis for dissection of the reaction kinetics into distinct pathways. The understanding of the resultant chemistry relies on the calculation of the reaction rate constants for the "two" reactive conformations in Scheme II chemistry, each substrate of which is a composite of many conformations.

V. CONCLUSION

In spite of a vast literature on conformational analysis, linear free energy relationships, and steric effects, much basic information needs to be obtained and quantitative models developed in these areas of chemistry. These powerful tools are especially lacking in newly emerging areas of organic chemistry, where remarkably elegant and esoteric reactions and stereochemistries may be observed many years before a proper understanding of the fundamental underlying principles are exposed. Thus, structural and conformational models were necessary to understand the conformations and reactivities of organotransition metal complexes of the type $(\eta^5\text{-}C_5H_5)M(Ph_3P)(CO/NO)R$ where R is an organic residue. The nontransferability of steric effect parameters from one reaction type (or substrate type) to another is another manifestation of the need for further studies of nonadditive kinetic effects. Two different models were presented which allow for the analysis, correlation, and prediction of kinetic and steric nonadditivity. These models were used for the study of the alkylation of substituted pyridines, quinolines, and simple cyclic and acyclic amines. To unravel the kinetics of conformationally mobile systems, and in particular, transformations involving molecules which react from two or more conformations, each of which give different products, the Curtin-Hammett principle and the Winstein-Holness equation were used in a novel, combined fashion. Calculation of reaction rate constants of particular conformations was then possible. Experimental determination and theoretical prediction of the chemical properties of the important conformations of molecules are still distant goals, but much progress has been made in laboratories throughout the world.

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