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Biotransformation of Drugs: Quantitative Structure–Activity Relationships for Barbiturates, Tertiary Amines, and Substituted Imidazoles

GEORGE L. TONG ˣ and ERIC J. LIEN

Abstract □ When using free energy-related physicochemical parameters, stimulation of NADPH oxidation by barbiturates and the *N*-oxidation of tertiary amines was found to be primarily dependent upon the lipophilic character of the substrates as measured by log *P*, where *P* is the partition coefficient from either 1-octanol–water or corn oil–water solvent systems. In contrast, the inhibition of epoxidation of aldrin by a series of substituted imidazoles appears to be much more dependent on electronic (σ) and steric (E_s) effects of the inhibitors.

Keyphrases □ Biotransformation, drug—quantitative structure–activity relationships for barbiturates, tertiary amines, and substituted imidazoles, physicochemical properties □ Structure–activity relationships—barbiturates, tertiary amines, and substituted imidazoles, biotransformation, physicochemical properties □ Barbiturates—effect on NADPH oxidation, quantitative structure–activity relationships, physicochemical properties □ Amines, tertiary—*N*-oxidation, quantitative structure–activity relationships, physicochemical properties □ Imidazoles, substituted—effect on epoxidation of aldrin, quantitative structure–activity relationships, physicochemical properties □ Metabolism, drug—quantitative structure–activity relationships for barbiturates, tertiary amines, and substituted imidazoles

Since early work (1, 2), the importance of lipophilic character in drug metabolism has been well established and documented (3–6). While there have been many elegant and well-designed *in vivo* and *in vitro* metabolism studies on single drugs, there have been relatively few good investigations of series of compounds to account for their differences in biotransformation in terms of their physicochemical properties. From the tremendous amount of published work on drug metabolism, there are relatively few good sets of data suitable for multiple regression analysis using free energy-related substituent constants. This paper reports the quantitative correlations obtained for the stimulation of NADPH oxidation by barbiturates, the *N*-oxidation of tertiary amines including chlorpromazine and morphine, and the inhibition of epoxidation of aldrin by substituted imidazoles.

EXPERIMENTAL

The microsomal oxidation data in Table I were obtained from the literature (7–9). The biological data were converted to log *C* or log 1/*C*, where *C* is the molar concentration required to elicit a standard biological response, *i.e.*, log (oxidation rate) in moles per minute per milligram or log $1/I_{50}$. The physicochemical constants used in the regression analysis (Table I) were obtained from the literature or calculated taking advantage of their additive and constitutive nature. All equations assembled in Table II were derived *via* the method of nonweighted least-squares fit using a computer program executed through a computer communicating terminal[1].

RESULTS AND DISCUSSION

Jannson *et al.* (7) studied the effects of a series of substituted barbituric acids on the rat hepatic microsomal monooxygenase system. They reported that there were no significant correlations of the microsomal oxidation with various measured physicochemical properties of the barbiturates such as the oil–water partition coefficient ($P_{o/w}$), pKa, cytochrome P_{450} dissociation constant (K_s), and maximal type I spectral change (ΔE). In contrast, they reported the importance of the partition coefficient in the inhibition of membrane-bound mitochondrial NADH oxidase. They suggested that although the lipid solubility was required for a substance to reach the microsomal cytochrome P_{450}, other properties of the barbiturates were important for determining the affinity of their interaction with the cytochrome system whereas the inhibition of the mitochondrial respiratory chain by uncoupling oxidative phosphorylation could be explained simply in terms of lipoid solubility.

In reanalyzing their results by using the free energy-related log *P* term instead of the partition coefficient itself, there was an excellent linear correlation (Eq. 2) with the 50% inhibition of NADH oxidation by the barbiturates. The coefficient or the slope associated with the log *P* term (0.88) is comparable to a similar dependence obtained for identical inhibition by barbiturates (10). The addition of either the pKa or the (log $P)^2$ term did not result in a statistically significant improvement in correlation.

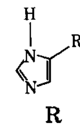
From the same work, only slightly improved correlations were found of the stimulation of microsomal NADPH oxidation by barbiturates with their free energy-related parameters (Eqs. 3–6). Closer inspection of the results of the regression analysis revealed that all allyl-substi-

[1] IBM 2741.

Table I—Microsomal Oxidation Data and Physicochemical Constants Used in Deriving the Equations in Table II

Inhibition of Mitochondrial NADH Oxidation		Stimulation of Microsomal NADPH Oxidation							
Log $1/I_{50}$		Log (Oxidation Rate)							
Obs.[a]	Calc.[b]	Obs.[c]	Calc.[d]	Calc.[e]	ΣE_s $(R_1 + R_2)$	Log $P_{o/w}$	ΔE	pKa	Compound
3.34	3.55	1.37	1.30	1.32	−0.79	0.88	0.045	8.35	Hexobarbital
3.28	3.25	1.13	1.10	1.16	−1.17	0.54	0.031	7.75	Heptabarbital
3.52	3.46	1.08	1.24	1.15	−1.20	0.78	0.030	8.05	Pentobarbital
3.74	3.67	—	—	—	−1.49	1.02	0.021	8.00	Secobarbital[f]
2.92	2.92	0.86	0.88	0.96	−0.86	0.16	0.013	7.65	Cyclobarbital
3.54	3.38	1.12	1.19	1.07	−0.42	0.69	0.023	7.95	Amobarbital
2.66	2.79	—	—	—	−0.83	0.02	0.0035	7.95	Aprobarbital[f]
3.11	3.00	0.97	0.94	0.92	−0.46	0.26	0.0095	7.95	Butabarbital
2.96	2.73	0.94	0.76	0.92	−1.20	−0.05	0.010	7.55	Vinbarbital
3.14	3.32	—	—	—	−2.10	0.62	0.006	7.80	Allylneopentylbarbituric acid[f]
3.30	3.25	—	—	—	−0.75	0.54	0.0085	7.85	Allylbutylbarbituric acid[f]
2.51	2.56	—	—	—	−0.72	−0.24	—	7.70	Diallylbarbituric acid[f]
2.66	2.78	0.87	0.79	0.85	−0.45	0.01	0.003	7.35	Phenobarbital
2.05	2.05	0.18	0.31	—	−0.14	−0.82	—	7.90	Barbital

Log (Oxidation Rate)				
Obs.[g]	Calc.[h]	Log P	pKa	Compound
−6.84	−6.96	0.27	9.27	Trimethylamine
−6.47	−6.50	1.77	10.02[i]	*N,N*-Dimethyl-*n*-butylamine
−6.11	−6.12	3.77	10.02[i]	*N,N*-Dimethyl-*n*-octylamine
−6.08	−6.07	4.27	10.02[i]	*N,N*-Dimethyl-*n*-nonylamine
−6.09	−6.00	5.77	10.02[i]	*N,N*-Dimethyl-*n*-dodecylamine
−6.31	−6.31	8.77	10.02[i]	*N,N*-Dimethyl-*n*-hexadecylamine
−6.30	−6.37	2.31	5.06	*N,N*-Dimethylaniline
−6.33	−6.27	2.81	5.23	*N,N*-Dimethyl-*p*-toluidine
−5.90	−6.01	5.35	10.02[i]	Chlorpromazine
−6.96	−6.80	0.76	9.85	Morphine

Inhibition of Microsomal Epoxidation of Aldrin by Imidazole Derivative										
Log $1/I_{50}$										
Obs.[j]	Calc.[k]	Calc.[l]	$E_{s\,(p)}$		Log P	$\sigma_{(p)}$	$\Sigma\sigma_{(m+p)}$	$F_{(p)}$	$R_{(p)}$	R
6.06	5.82	5.88	H	1.24	2.03	0.00	0.00	0.00	0.00	$C_6H_5OCH_2$—
5.94	6.07	6.07	H	1.24	2.62	0.00	0.00	0.00	0.00	2-$ClC_6H_4OCH_2$—
5.62	5.70	5.59	Cl	0.18	2.73	0.23	0.23	0.41	−0.15	4-$ClC_6H_4OCH_2$—
6.19	6.13	6.13	H	1.24	2.78	0.00	0.00	0.00	0.00	2-$BrC_6H_4OCH_2$—
5.68	5.67	5.67	Br	0.00	3.05	0.23	0.23	0.44	−0.17	4-$BrC_6H_4OCH_2$—
5.66	5.85	5.89	H	1.24	2.04	0.00	0.00	0.00	0.00	2-$FC_6H_4OCH_2$—
6.28	6.20	6.18	H	1.24	2.95	0.00	0.00	0.00	0.00	2-$IC_6H_4OCH_2$—
5.84	5.92	6.02	Cl	0.18	4.09	0.23	0.09	0.41	−0.15	3,5-$(CH_3)_2$,4-$ClC_6H_2OCH_2$—
6.10	6.09	6.09	H	1.24	2.67	0.00	0.00	0.00	0.00	$C_6H_5SCH_2$—
6.07	5.94	6.07	I	−0.20	3.93	0.28	0.28	0.40	−0.19	4-$IC_6H_4SCH_2$—
5.30	5.28	5.30	CH_3O	0.99	2.63	−0.27	−0.27	0.26	−0.51	4-$CH_3OC_6H_4SCH_2$—
6.13	6.17	5.98	Cl	0.18	3.96	0.23	0.23	0.41	−0.15	2,4-$Cl_2C_6H_3SCH_2$—
6.26	6.28	6.25	H	1.24	3.17	0.00	0.00	0.00	0.00	$C_6H_5CH_2SCH_2$—

[a] I_{50} is the molar concentration required to inhibit 50% NADH oxidation (7). [b] Calculated from Eq. 2. [c] The oxidation rate is the increase in substrate-induced NADPH in moles per minute per milligram of protein (7). [d] Calculated from Eq. 9. [e] Calculated from Eq. 10. [f] Allyl-containing barbiturate. [g] The oxidation rate of substrate-dependent NADPH in moles per minute per milligram of protein (8). [h] Calculated from Eq. 12. [i] Estimated from the pKa of *N,N*-dimethyl-*n*-butylamine. [j] I_{50} is the molar concentration required to inhibit 50% epoxidation of aldrin (9). [k] Calculated from Eq. 21. [l] Calculated from Eq. 22.

tuted barbiturates were poorly predicted, and they stimulated the rate of metabolism to a lesser extent than the nonallyl barbiturates.

In a well-designed controlled study, allyl-containing barbiturates administered to rats treated with a microsomal enzyme inducer caused a rapid destruction of the hemeprotein cytochrome P_{450}, while corresponding nonallyl barbiturates did not have this effect (11). The results suggested that the allyl group in the biotransformation process is probably converted to a highly reactive epoxide intermediate, which leads to the reduction of the terminal oxidase involved in drug metabolism (11).

Upon deletion of the allyl barbiturates from the regression analysis, two highly significant equations (Eqs. 9 and 10) were obtained correlating the log of the oxidation rate with either the log $P_{o/w}$ or the maximal type I spectral change (ΔE). The coefficient of 0.58 in Eq. 9 associated with log $P_{o/w}$ is within the range (0.60 ± 0.1) of the log $P_{\text{octanol-water}}$ reported for various types of drug metabolism (6), as well as for the nonspecific binding of organic compounds to a wide variety of proteins and proteinaceous materials (12–14). The relationship between log P values measured in these two solvent systems was reported previously (15) to be log $P_{\text{oil-water}} = 1.099 \log P_{\text{octanol-water}} - 1.310$ with $n = 65$, $r = 0.98$, and $s = 0.27$.

Table II—Equations Correlating Various Microsomal Oxidations with Physicochemical Constants

Equation	n^a	s^b	r^c	Equation Number
Inhibition of beef heart submitochondrial NADH oxidation by barbiturates				
$\log 1/I_{50} = 0.68\ \text{pKa} - 2.25$	14	0.446	0.372	1
$= 0.88 \log P_{(\text{corn oil-water})} + 2.78$	14	0.133	0.961	2
Stimulation of rat liver microsomal NADPH oxidation by barbiturates				
$\log(\text{oxidation rate}) = 0.05\ \Sigma E_{s(R_1+R_2)} + 0.91$	14	0.317	0.082	3
$= 0.27\ \text{pKa} - 1.25$	14	0.310	0.223	4
$= 0.36 \log P_{(\text{corn oil-water})} + 0.75$	14	0.256	0.593	5
$= 13.16\ \Delta E_{(\max\ \text{type I})} + 0.72$	12	0.175	0.718	6
Exclusion of allyl-containing barbiturates				
$\log(\text{oxidation rate}) = 0.29\ \text{pKa} - 1.31$	9	0.338	0.273	7
$= 0.46\ \Sigma E_{s(R_1+R_2)} + 0.61$	9	0.294	0.547	8
$= 0.58 \log P_{(\text{corn oil-water})} + 0.79$	9	0.116	0.944	9
$= 11.25\ \Delta E_{(\max\ \text{type I})} + 0.81$	8	0.063	0.939	10
Pork liver microsomal NADPH dependent *N*-oxidation of tertiary amines				
$\log(\text{oxidation rate}) = 0.09 \log P - 6.61$	10	0.269	0.672	11
$= -0.03 (\log P)^2 + 0.37 (\log P) - 7.06$ $\log P_o = 5.69\ (5.12 - 6.64)^d$	10	0.106	0.962	12
Inhibition of rat liver microsomal epoxidation of aldrin by imidazole derivatives				
$\log 1/I_{50} = 0.11 \log P + 5.61$	13	0.298	0.247	13
$= 0.12\ E_{s(p)} + 5.84$	13	0.299	0.239	14
$= 0.35\ \sigma_{(p)} + 5.91$	13	0.302	0.186	15
$= 0.43\ \Sigma\sigma_{(m+p)} + 5.91$	13	0.300	0.219	16
$= 0.42\ E_{s(p)} + 0.37 \log P + 4.52$	13	0.249	0.637	17
$= 2.22\ \sigma_{(p)} + 0.61\ E_{s(p)} + 5.31$	13	0.227	0.713	18
$= 2.07\ \Sigma\sigma_{(m+p)} + 0.53\ E_{s(p)} + 5.40$	13	0.232	0.696	19
$= 1.96\ \sigma_{(p)} + 0.81\ E_{s(p)} + 0.32 \log P + 4.22$	13	0.166	0.872	20
$= 2.15\ \Sigma\sigma_{(m+p)} + 0.86\ E_{s(p)} + 0.39 \log P + 4.00$	13	0.125	0.930	21
$= -1.75\ F_{(p)} + 0.78\ R_{(p)} - 0.29\ E_{s(p)} + 0.32 \log P + 5.58$	13	0.147	0.914	22

[a] The number of data points or compounds used in the regression analysis. [b] The standard deviation from the regression. [c] The correlation coefficient. [d] The 95% confidence interval on $\log P_O$.

The *N*-oxidation rates of various amines were studied using a purified microsomal mixed function amine oxidase system (8). A relationship was found between the oxidation rate and the chain length up to nine carbons for the tertiary amines studied (8).

Analysis of only the substituted *N,N*-dimethyl tertiary amines, forming detectable corresponding *N*-oxide metabolites, showed a highly statistically significant (99.95 percentile level) parabolic equation (Eq. 12) using the *F* test. Included in the regression analysis were chlorpromazine and morphine, which are also tertiary amines. When these compounds were tested under the same conditions, they gave the corresponding *N*-oxide and fit reasonably well into the regression curve (Fig. 1). By setting the $d \log(\text{oxidation rate})/(d \log P) = 0$, the optimal $\log P_o$ of 5.69 for maximal *N*-oxidation with a 95% confidence interval of 5.12–6.64 was obtained. Chlorpromazine, with a $\log P$ of 5.35, is close to the $\log P_o$, and it was metabolized at the fastest rate among all of the compounds examined. The $\log P$ values are for the unprotonated forms, so under physiological conditions at pH 7.4, most aliphatic tertiary amines would be protonated and the $\log P$ of the charged species would be approximately 3 log units lower (16). The addition of the pKa term to account for differences in the basicity of aromatic *versus* aliphatic tertiary amines did not significantly improve the correlation.

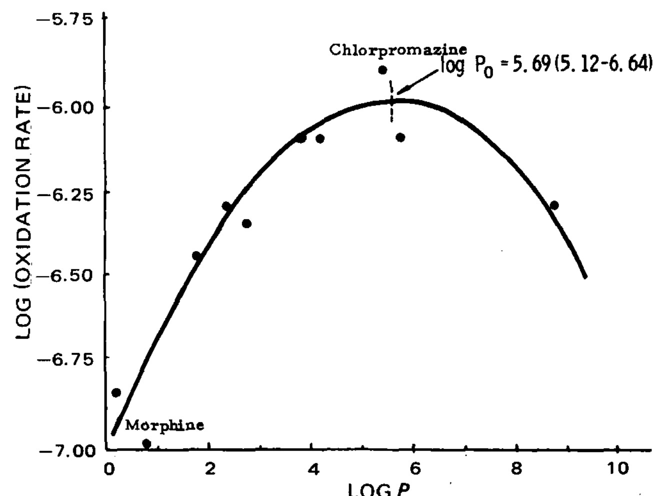


Figure 1—*Parabolic dependence of the* N-*oxidation rate of tertiary amines on log* P *(Eq. 12).*

In contrast to the relatively nonspecific microsomal oxidations where the lipophilicity of the substrate is of primary importance, the inhibition of the rat liver microsomal epoxidation of aldrin by substituted imidazoles (9) appears to be much more specific on both electronic and steric parameters.

The best equations obtained from all possible combinations of linear and quadratic equations are Eqs. 20–22. In Eq. 21, the positive coefficient on the summation of Hammett's (σ) constant for both the *meta*- and *para*-positions on the benzene ring suggests that an electron-withdrawing group enhances the inhibitory activity. The positive dependence on Taft's (E_s) steric constant suggests the importance of a small substituent in the *para*-position. The addition of $\log P$ of the whole molecule is statistically significant but is only of secondary importance. This equation reflects the importance of electronic and steric effects in the inhibition of drug metabolism, probably due to greater specificity at the active site.

Similar dependence on σ and E_s also was noted previously for several types of enzyme inhibition such as carbonic anhydrase, D-amino acid oxidase, and monoamine oxidase by various inhibitors (17). Swain's and Lupton's *F* and *R* aromatic substituent constants (18) for field and resonance effects, respectively, gave comparable but not better correlations (Eq. 22).

CONCLUSION

In summary, it is gratifying to see that the fairly complicated biotransformations of various drugs by different microsomal systems can be well correlated with a few physicochemical constants. The results obtained from the available data suggest that the modification of organic compounds by microsomal enzymes can be understood in terms of their physicochemical properties in a quantitative way. This type of approach in the future may be useful in the understanding of drug metabolism and possibly aid the medicinal chemist in drug design *via* molecular modification to affect biotransformation.

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Effect of Topically Applied Pilocarpine on Tear Film pH

A. LONGWELL [x], S. BIRSS, N. KELLER, and D. MOORE

Abstract □ Changes in tear film pH were observed during the 1st hr after instillation of pilocarpine in various dosage forms to the rabbit eye. In anesthetized rabbits, with periodic blinking induced electrically, commercial formulations of pilocarpine salts applied as drops or a spray acutely lowered tear film pH by 1.1–1.6 pH units. The pH remained below pretreatment levels for 45–>60 min after instillation. Pilocarpine base, administered continuously at the rates of 20 or 80 μg/hr from ocular therapeutic systems, had little or no effect on tear film pH in this same animal preparation. The reduction in tear film pH produced by pilocarpine eyedrops or spray solution is attributable to the acid pH and buffer capacity of these solutions. Delivery of pilocarpine base without pH change was achieved with ocular therapeutic systems, because the drug (pKa = 7.07) was delivered free, or virtually so, of excipients. These observed differences in tear film pH after application may partially explain the four- to eightfold reduction in total effective pilocarpine dose with ocular therapeutic systems compared to eyedrops or spray, since the cornea is less permeable to ionized than to unionized molecules.

Keyphrases □ Pilocarpine—topically applied base and salts, effect on tear film pH, rabbits □ Tear film pH—effect of topically applied pilocarpine, base and salts compared, rabbits □ pH—tear film, effect of topically applied pilocarpine, base and salts compared, rabbits □ Ophthalmic cholinergic agents—pilocarpine base and salts, topically applied, effect on tear film pH, rabbits

The pH of the tear film is of interest to ophthalmic pharmacologists for two reasons. Tear pH is an important factor in the penetration of any topically applied ophthalmic drug that is a weak base, since the cornea is less permeable to ionized than to unionized molecules. In addition, well-buffered acid solutions are known to cause more sensation of stinging or burning to the eye than do weakly buffered acid solutions, because the concentrated acid buffer overwhelms the *in vivo* buffer capacity of tear film.

The major buffering system in extracellular fluids, including tears, is the bicarbonate system. Tear film concentration of bicarbonate is the same as that of plasma. However, the total buffering capacity of tear film is obviously very small, since its volume is only about 7 μl. Thus, the addition of eyedrop solutions such as 1–4% pilocarpine at pH 4–5, in volumes five to 10 times that of the tear film, might be expected to overwhelm, for a time, the buffering capacity of the tears.

Pilocarpine is dispensed as a nitrate or hydrochloride in solutions ranging from 0.5 to 10% (0.025–0.5 *M*); even at the commonly prescribed concentration of 2% (0.1 *M*), a solution of pilocarpine nitrate alone, which has an equilibrium pH of 3.9, is a fairly concentrated buffer. The pH of most pilocarpine ophthalmic solutions, however, is adjusted to 4.5–5.5, but no higher, for reasons of drug stability in solution. The topical application of these low pH solutions of pilocarpine, either in eyedrops or in sprays, should reduce tear film pH for some time after administration.