The polymer still retains its linearity; upon addition of any precipitant to sulfathiazole, the whole molecule is coiled and coacervated.

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Quantitative Structure–Activity Relationships in Drug Metabolism and Disposition: Pharmacokinetics of *N*-Substituted Amphetamines in Humans

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Abstract □ Pharmacokinetic data of 15 *N*-alkyl-substituted amphetamines in humans have been the object of a retrospective quantitative structure–activity relationship study. The urinary excretion of amphetamines was shown to decrease with increasing lipophilicity; the correlation equations revealed that, for identical lipophilicities, tertiary amines are excreted faster than secondary amines, which are excreted faster than primary amines. The apparent *n*-heptane–pH 7.4 buffer partition coefficient correlates better with urinary excretion than does the true *n*-octanol–water partition coefficient, probably because it includes a pKa term that accounts for the fraction of the drug present in the tubules as nonionic species. The *N*-dealkylation rate increases with increasing lipophilicity of the substrates (enhanced enzyme affinity) but decreases with increasing bulk of the *N*-substituent that is split off (steric hindrance of initial C_α-hydroxylation).

Keyphrases □ Quantitative structure–activity relationships—*N*-substituted amphetamines, pharmacokinetics, humans □ Amphetamines, *N*-substituted—pharmacokinetics, quantitative structure–activity relationships, humans □ Pharmacokinetics—*N*-substituted amphetamines, quantitative structure–activity relationships, humans

Quantitative structure–activity relationships have many pharmacological and toxicological applications. The correlation equations obtained in such studies often provide valuable steps in the rational design of improved drugs (1).

Suitable results of drug metabolism studies also can provide a valuable biological input to quantitative structure–activity relationship studies. While the results thus obtained could help in designing drugs with improved metabolic profiles, previous investigations (2–5) concentrated entirely on interpreting the correlation equations in terms of reaction mechanisms and of the structural factors influencing the biological response.

One prerequisite of any quantitative structure–activity relationship investigation is the need for quantitative and reliable biological data. This fact may help to explain why applications of quantitative structure–activity relationships to drug metabolism and disposition have been based almost exclusively on results from *in vitro* studies (*e.g.*, protein binding, drug–enzyme interactions, and parameters of *in vitro* biotransformation). In contrast, few, if any, *in vivo* studies have led to successful quantitative structure–activity relationship interpretations.

The present report describes the application of quantitative structure–activity relationship methodology to the results of a pharmacokinetic study of *N*-alkyl-substituted amphetamine derivatives in humans (6). The thoroughness of the work of the previous investigators, the quantitative nature of results, the number (15) of molecules investigated, and the large spread in the biological responses made this study an attractive candidate for a quantitative interpretation in terms of molecular properties. Furthermore, the previous investigators measured the apparent

Table I—Physicochemical and Structural Parameters of Amphetamine and Derivatives

	Compound	Log P_H[a]	$f_{RR'}$[b]	V_R[c]	NH[d]	$C_\alpha H$[e]
I	Amphetamine	−2.26	0.94	—	2	—
II	*N*-Methyl	−1.51	1.17	13.67	1	3
III	*N*-Ethyl	−0.92	1.69	23.90	1	2
IV	*N*-*n*-Propyl	−0.20	2.21	34.13	1	2
V	*N*-2-Propyl	−0.41	2.21	34.12	1	1
VI	*N*-*n*-Butyl	−0.32	2.73	44.36	1	2
VII	*N*-2-Butyl	0.07	2.73	44.35	1	1
VIII	*N*-Benzyl	3.18	2.83	56.07	1	2
IX	*N*,*N*-Dimethyl	−0.27	1.40	13.67	0	3
X	*N*,*N*-Diethyl	0.58	2.44	23.90	0	2
XI	*N*,*N*-Di-*n*-propyl	2.38	3.48	34.13	0	2
XII	*N*,*N*-Di-*n*-butyl	3.83	4.52	44.36	0	2
XIII	*N*-Ethyl-*N*-methyl	−0.09	1.92	13.67[f]	0	3[f]
				23.90[g]		2[g]
XIV	*N*-Methyl-*N*-*n*-propyl	0.45	2.44	13.67[f]	0	3[f]
				34.13[g]		2[g]
XV	*N*-*n*-Butyl-*N*-methyl	1.44	2.96	13.67[f]	0	3[f]
				44.36[g]		2[g]

[a] P_H is the apparent *n*-heptane–water partition coefficient measured at pH 7.4 (6). [b] Hydrophobic fragmental constant of the two nitrogen substituents (hydrogen and/or alkyl) (7). [c] Volume in milliliters per mole of substituent that is cleaved by *N*-dealkylation, calculated according to Bondi (9). [d] Number of hydrogen atoms on the nitrogen. [e] Number of hydrogen atoms on the α-carbon of substituent that is cleaved by *N*-dealkylation. [f] *N*-Methyl group. [g] *N*-Alkyl group.

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Table II—Percent of Amphetamine Derivatives Excreted Unchanged (PEU): Experimental *versus* Calculated Values

	Log PEU								
	Subject 1			Subject 2			Subject 3		
Derivative	Exp.[a]	Calc.[b]	Residual	Exp.[a]	Calc.[c]	Residual	Exp.[a]	Calc.[d]	Residual
I	1.78	1.82	−0.04	1.76	1.84	−0.08	1.79	2.11	−0.32
II	1.83	1.78	0.05	1.79	1.77	0.02	1.69	1.72	−0.03
III	1.68	1.68	0.00	1.66	1.66	0.00	1.16	1.42	−0.26
IV	1.51	1.50	0.01	1.49	1.47	0.02	1.08	1.05	0.03
V	1.59	1.56	0.03	1.60	1.53	0.07	1.35	1.15	0.20
VI	0.87	1.31[e]	−0.44	0.76	1.28[e]	−0.52	0.29	0.78	−0.49
VII	1.28	1.41	−0.13	1.34	1.38	−0.04	1.10	0.91	0.19
VIII	−0.23	−0.45	0.22	−0.27	−0.33	0.06	−0.78	−0.70	−0.08
IX	1.59	1.52	0.07	1.61	1.49	0.12	1.33	1.08	0.25
X	1.60	1.20	0.40	1.44	1.18	0.26	1.29	0.64[e]	0.65
XI	0.25	0.17	0.08	0.17	0.22	−0.05	−0.28	−0.29	0.01
XII	−1.16	−1.02	−0.14	−0.82	−0.85	0.03	−1.12	−1.04	−0.08
XIII	1.54	1.46	0.08	1.58	1.43	0.15	1.18	0.99	0.19
XIV	1.38	1.26	0.12	1.40	1.23	0.17	0.87	0.71	0.16
XV	0.47	0.77	−0.30	0.57	0.78	−0.21	−0.21	0.20	−0.41

[a] Data from Ref. 6. [b] Calculated according to Eq. 2. [c] Calculated according to Eq. 6. [d] Calculated according to Eq. 9. [e] Outlier (outside ±2 *SD*).

Table III—Rate Constant of Excretion (EXC) in Hours^{-1} of Amphetamine Derivatives: Experimental *versus* Calculated Values

	Log EXC								
	Subject 1			Subject 2			Subject 3		
Derivative	Exp.[a]	Calc.[b]	Residual	Exp.[a]	Calc.[c]	Residual	Exp.[a]	Calc.[d]	Residual
I	−1.17	−1.14	−0.03	−1.10	−1.00	−0.10	−1.09	−1.20	0.11
II	−1.15	−1.02	−0.13	−1.04	−0.93	−0.11	−1.14	−1.18	0.04
III	−1.15	−1.22	0.07	−1.12	−1.18	0.06	−1.55	−1.42	−0.13
IV	−1.31	−1.46	0.15	−1.28	−1.47	0.19	−1.86	−1.71	−0.15
V	−1.27	−1.39	0.12	−1.28	−1.39	0.11	−1.47	−1.63	0.16
VI	−1.75	−1.63	−0.12	−1.89	−1.69	−0.20	−2.33	−1.93	−0.40
VII	−1.59	−1.55	−0.04	−1.54	−1.58	0.04	−1.68	−1.82	0.14
VIII	−2.61	−2.58	−0.03	−2.76	−2.86	0.10	−3.07	−3.10	0.03
IX	−1.17	−1.07	−0.10	−1.16	−1.07	−0.09	−1.41	−1.36	0.05
X	−1.19	−1.35	0.16	−1.37	−1.42	0.05	−1.38	−1.71	0.33
XI	−2.36	−1.95[e]	−0.41	−1.55	−2.16[e]	0.61	−2.79	−2.44	−0.35
XII	—[f]	—	—	−3.20	−2.76	−0.44	—[f]	—	—
XIII	−1.28	−1.13	−0.15	−1.16	−1.15	−0.01	−1.55	−1.43	−0.12
XIV	−1.32	−1.31	−0.01	−1.34	−1.37	0.03	−1.79	−1.65	−0.14
XV	−2.04	−1.64[e]	−0.40	−2.03	−1.78	−0.25	−2.72	−2.06[e]	−0.66

[a] Data from Ref. 6. [b] Calculated according to Eq. 12. [c] Calculated according to Eq. 15. [d] Calculated according to Eq. 18. [e] Outlier (outside ±2 *SD*). [f] Data not available.

partition coefficient of their compounds and established graphical correlations for limited subsets of observations.

EXPERIMENTAL

Table I lists the 15 molecules investigated. Two parameters are used as a measure of lipophilicity: (*a*) the apparent *n*-heptane–water partition coefficient measured at pH 7.4 (6), and (*b*) the sum of the hydrophobic fragmental constants of the two nitrogen substituents (hydrogen and/or alkyl) (7). The latter parameter represents the incremental contributions of molecular fragments to the true *n*-octanol–water partition coefficient (8).

The degree of substitution on the nitrogen atom (primary, secondary, or tertiary) is taken into account by the structural descriptor NH, *i.e.*, the number of hydrogen atoms on the nitrogen. Two parameters specifically consider the *N*-alkyl substituent that is cleaved from the molecule: the volume of the substituent, calculated according to Bondi (9), and the number of hydrogen atoms on the α-carbon.

Donike *et al.* (6) determined three biological responses that are valuable parameters in this study. They are: (*a*) the cumulative urinary excretion of unchanged drug expressed as the percent of the administered dose [percent excreted unchanged (PEU)]; (*b*) the rate constant of urinary excretion, EXC, in hours^{-1}; and (*c*) the rate constant of the first *N*-dealkylation step, DEA, in hours^{-1}.

Three subjects were used in the study of Donike *et al.* (6). Subjects 1 and 2 were kept under acidic urinary control by ingestion of ammonium chloride (urinary pH values were 5.0–5.2 and 4.9–5.1, respectively). The urinary pH of Subject 3 was not controlled and was comparatively higher (5.4–5.7). The individual values of log PEU, log EXC, and log DEA for Subjects 1–3 are reported in Tables II–IV. These data provided the input for the dependent variables in the present calculations.

The multiple linear regression analyses were performed on a computer[1] using the SPSS program (10) with a stepwise method. The program calculates the regression coefficients of all independent variables and their standard deviation (given in parentheses) and the constant term (intercept). The statistics performed include the squared multiple correlation coefficient, r^2, the standard deviation of the equation, *s*, and the *F* test. Testing the null hypotheses for each regression coefficient individually is done by the Student *t* test; these values are not reported here, but all variables included in Eqs. 1–28 are significant at the probability level of 0.05 or better.

Table V gives the correlation matrixes for 15 observations (Eqs. 1–19) and for 17 observations (Eqs. 20–28).

RESULTS AND DISCUSSION

Cumulative Urinary Excretion of Unchanged Drugs—The significant correlation equations derived for log PEU are shown in Table VI, revealing that this biological response depends heavily on the lipophilicity of the molecules as assessed by the apparent *n*-heptane–water partition coefficient (Eqs. 1, 5, and 9). These equations indicate that the total excretion of unchanged drug increases with decreasing log P_H; *i.e.*, high hydrophilicity favors fast excretion and limited biotransformation. This linear correlation can be improved by the inclusion of a squared term to yield parabolic equations (Eqs. 2 and 6). The optimal log P_H value thus determined is that of amphetamine for Subject 1, while the value for Subject 2 is that of a hypothetical derivative somewhat more hydrophilic than amphetamine.

However, Eqs. 2 and 6 are not truly meaningful from a physical point of view. It is reasonable to expect that hypothetical derivatives that are

[1] Cyber, CDC, Federal Institute of Technology and the University of Lausanne

Table IV—Rate Constant of First *N*-Dealkylation Step (DEA) in Hours^{-1} of Amphetamine Derivatives: Experimental *versus* Calculated Values

	Log DEA								
	Subject 1			Subject 2			Subject 3		
Derivative	Exp.[a]	Calc.[b]	Residual	Exp.[a]	Calc.[c]	Residual	Exp.[a]	Calc.[d]	Residual
II	−2.07	−1.83	−0.24	−1.84	−1.97	0.14	−1.90	−1.62	−0.28
III	−1.76	−1.82	0.06	−1.69	−1.80	0.11	−1.94	−1.69	−0.25
IV	−1.69	−1.77	0.08	−1.51	−1.63	0.12	−1.69	−1.73	0.04
V	−1.69	−1.82	0.13	−1.66	−1.63	−0.03	−1.63	−1.80	0.17
VI	−1.45	−1.77[e]	0.32	−1.53	−1.46	−0.07	−1.70	−1.83	0.13
VII	−1.82	−1.84	0.02	−1.71	−1.46	−0.25	−1.58	−1.91	0.33
VIII	−1.15	−1.15	0.00	−1.49	−1.64	0.15	−1.25	−1.27	0.02
IX	−1.63	−1.48	−0.15	−1.57	−1.80	0.23	−1.34	−1.25	−0.09
X	−1.20	−1.39	0.19	−1.26	−1.24	−0.02	−0.81	−1.25[e]	0.44
XI	−0.78	−1.04	0.26	−0.74	−0.68	−0.06	−0.80	−0.96	0.16
XII	—[f]	—	—	0.30	−0.12[e]	0.42	—[f]	—	—
XIII[g]	−1.61	−1.43	−0.18	−1.52	−1.41	−0.11	−1.25	−1.19	−0.06
XIII[h]	−1.70	−1.58	−0.12	−1.55	−1.63	0.08	−1.56	−1.45	−0.11
XIV[g]	−1.04	−1.28	0.24	−1.16	−1.03	−0.13	−0.79	−1.03	0.24
XIV[h]	−1.50	−1.58	0.08	−1.53	−1.46	−0.07	−1.42	−1.54	0.12
XV[g]	−0.94	−1.00	0.06	−0.82	−0.64	−0.18	−0.80	−0.74	−0.06
XV[h]	−1.54	−1.46	−0.08	−1.64	−1.29	−0.35	−1.69	−1.50	−0.19

[a] Data from Ref. 6. [b] Calculated according to Eq. 20. [c] Calculated according to Eq. 24. [d] Calculated according to Eq. 26. [e] Outlier (outside ±2 *SD*). [f] Data not available. [g] *N*-Demethylation. [h] *N*-Dealkylation.

Table V—Correlation Matrix for 15 Observations[a] (Eqs. 1–19)

	$(\text{Log P}_H)^2$	Log P_H	$f_{RR'}$	V_R	$C_\alpha H$	NH	Log PEU_1	Log PEU_2	Log PEU_3	Log EXC_1	Log EXC_2	Log EXC_3	Log DEA_1	Log DEA_2
Log P_H	0.69	—	—	—	—	—	—	—	—	—	—	—	—	—
	0.84													
$f_{RR'}$	0.58	0.91	—	—	—	—	—	—	—	—	—	—	—	—
	0.71	*0.89*												
V_R	0.53	0.55	0.58	—	—	—	—	—	—	—	—	—	—	—
	0.49	*0.56*	*0.59*											
$C_\alpha H$	−0.08	−0.11	−0.32	−0.74	—	—	—	—	—	—	—	—	—	—
	−0.06	*−0.11*	*−0.30*	*−0.72*										
NH	−0.03	−0.54	−0.49	0.48	−0.53	—	—	—	—	—	—	—	—	—
	−0.07	*−0.33*	*−0.27*	*0.36*	*−0.43*									
Log PEU_1	−0.85	−0.93	−0.88	−0.58	0.11	0.33	–	–	–	–	–	–	–	–
	−0.90	*−0.95*	*−0.89*	*−0.59*	*0.10*	*0.19*								
Log PEU_2	−0.83	−0.94	−0.87	−0.62	0.13	0.31	0.99	—	—	—	—	—	—	—
	−0.89	*−0.96*	*−0.88*	*−0.62*	*0.11*	*0.16*	*0.99*							
Log PEU_3	−0.74	−0.95	−0.87	−0.56	0.06	0.38	0.97	0.98	—	—	—	—	—	—
	−0.81	*−0.94*	*−0.86*	*−0.59*	*0.06*	*0.21*	*0.97*	*0.98*						
Log EXC_1	−0.71	−0.88	−0.77	−0.58	0.13	0.14	0.99	0.99	0.96	—	—	—	—	—
	−0.82	*−0.91*	*−0.80*	*−0.60*	*0.12*	*0.01*	*0.99*	*0.97*	*0.96*					
Log EXC_2	−0.81	−0.88	−0.81	−0.65	0.16	0.21	0.95	0.94	0.92	0.88	—	—	—	—
	−0.86	*−0.89*	*−0.82*	*−0.65*	*0.15*	*0.06*	*0.95*	*0.95*	*0.92*	*0.88*				
Log EXC_3	−0.55	−0.90	−0.82	−0.52	0.05	0.25	0.97	0.96	0.99	0.95	0.87	—	—	—
	−0.70	*−0.90*	*−0.82*	*−0.56*	*0.05*	*0.08*	*0.98*	*0.96*	*0.99*	*0.96*	*0.88*			
Log DEA_1	0.45	0.83	0.78	0.06	0.17	−0.61	−0.71	−0.72	−0.75	−0.66	−0.53	−0.73	—	—
	0.46	*0.80*	*0.74*	*0.06*	*0.18*	*−0.48*	*−0.67*	*−0.69*	*−0.69*	*−0.63*	*−0.51*	*−0.67*		
Log DEA_2	0.73	0.80	0.86	0.17	0.07	−0.61	−0.81	−0.78	−0.76	−0.54	−0.70	−0.62	0.93	—
	0.73	*0.76*	*0.81*	*0.12*	*0.10*	*−0.47*	*−0.77*	*−0.74*	*−0.69*	*−0.47*	*−0.66*	*−0.52*	*0.92*	
Log DEA_3	0.23	0.65	0.58	−0.22	0.31	−0.84	−0.44	−0.43	−0.45	−0.39	−0.29	−0.41	0.88	0.86
	0.23	*0.58*	*0.50*	*−0.26*	*0.33*	*−0.65*	*−0.36*	*−0.37*	*−0.36*	*−0.32*	*−0.22*	*−0.32*	*0.87*	*0.87*

[a] The italicized numbers are the correlation matrix for 17 observations (Eqs. 20–28).

markedly more hydrophilic than amphetamine will simply be excreted totally unchanged (log PEU = 2.0); in this region, a plot of log P_H *versus* log PEU should be a horizontal line, and the true nature of the mathematical relationship can be envisioned as a bilinear function. However, testing of this hypothesis is not feasible due to a lack of suitable observations. In any case, extrapolation of Eqs. 2 and 6 to hypothetical compounds that are more hydrophilic than amphetamine is misleading.

For Subject 3, the inclusion of a squared term is not significant, indicating that the lack of urinary pH control alters not only the magnitude of excretion but apparently also the nature of the mathematical relationship between elimination and lipophilicity.

Equations 3 and 7 explore another aspect of the structure–activity relationships: total excretion of unchanged drug increases with the number of *N*-substituents once the lipophilicity of the molecules is accounted for by the log P_H term. The correlation between log PEU and NH alone is positive (Table V), but Eqs. 3 and 7 indicate that, for identical lipophilicities, tertiary amines are excreted faster and are less metabolized than are secondary amines. However, such a relationship holds only in the case of urinary pH control, with the inclusion of the NH parameter being nonsignificant for Subject 3.

Replacement of log P_H by $f_{RR'}$, a measure of the *n*-octanol–water partition coefficient of the nonprotonated bases, to yield Eqs. 4, 8, and 10 results in less favorable statistics, as evidenced by smaller r^2 values, and considerably larger standard deviations. Also, the inclusion of any other variable in Eqs. 4, 8, and 10 is nonsignificant.

The better correlations displayed by log P_H as compared to $f_{RR'}$ probably is due to the fact the log P_H includes a pKa term, thus accounting for the fraction of drug present in the tubules as nonionic species. This fraction is no less important than the lipophilicity of the neutral form in influencing the urinary excretion of amphetamines.

The best equations for log PEU_i are Eqs. 2, 6, and 9. A comparison of experimental and calculated log PEU_i values is given in Table II.

Rate Constant of Urinary Excretion—The significant correlation equations obtained for log EXC are given in Table VII. As with the previous examples, this biological response is mainly dependent on lipophilicity. Equations 11, 14, and 17 show that the rate of excretion increases with decreasing log P_H, confirming that high hydrophilicity favors fast excretion, presumably due to minimal tubular reabsorption. The relationship is linear, with the parabolic equations being nonsignificant.

Table VI—Correlation Equations for Log PEU (Percent Excreted Unchanged) in Subjects 1–3

Equation	Dependent Variable	$(\text{Log } P_H)^2$	Log P_H	NH	$f_{RR'}$	Intercept	n	r^2	s	F
1	Log PEU_1	—	−0.486 (±0.057)	—	—	1.28 (±0.09)	15	0.868	0.330	72.2
2[a]	Log PEU_1	−0.0771 (±0.0201)	−0.345 (±0.053)	—	—	1.43 (±0.07)	15	0.947	0.220	88.7
3	Log PEU_1	—	−0.556 (±0.058)	−0.342 (±0.153)	—	1.51 (±0.13)	15	0.912	0.283	51.7
4	Log PEU_1	—	—	—	−0.829 (±0.137)	3.04 (±0.35)	15	0.770	0.435	36.7
5	Log PEU_2	—	−0.458 (±0.050)	—	—	1.27 (±0.08)	15	0.886	0.286	85.3
6[b]	Log PEU_2	−0.0643 (±0.0184)	−0.341 (±0.048)	—	—	1.40 (±0.07)	15	0.949	0.201	92.5
7	Log PEU_2	—	−0.530 (±0.045)	−0.352 (±0.119)	—	1.52 (±0.10)	15	0.939	0.219	77.4
8	Log PEU_2	—	—	—	−0.769 (±0.130)	2.90 (±0.33)	15	0.761	0.414	35.1
9	Log PEU_3	—	−0.517 (±0.053)	—	—	0.943 (±0.088)	15	0.896	0.307	94.4
10	Log PEU_3	—	—	—	−0.865 (±0.145)	2.77 (±0.37)	15	0.764	0.461	35.6

[a] Optimal log $P_H = -2.24$. [b] Optimal log $P_H = -2.65$.

Table VII—Correlation Equations for Log EXC (Log Rate Constant of Excretion) in Subjects 1–3

Equation	Dependent Variable	Log P_H	NH	$f_{RR'}$	Intercept	n	r^2	s	F
11	Log EXC_1	−0.257 (±0.041)	—	—	−1.41 (±0.07)	14	0.781	0.237	39.2
12	Log EXC_1	−0.332 (±0.027)	−0.362 (±0.071)	—	−1.16 (±0.06)	14	0.940	0.130	78.1
13	Log EXC_1	—	—	−0.616 (±0.036)	—	14	0.960	0.332	288.0
14	Log EXC_2	−0.335 (±0.056)	—	—	−1.44 (±0.09)	15	0.767	0.321	36.2
15	Log EXC_2	−0.412 (±0.053)	−0.373 (±0.139)	—	−1.18 (±0.12)	15	0.864	0.257	31.8
16	Log EXC_2	—	—	−0.655 (±0.042)	—	15	0.953	0.384	243.0
17	Log EXC_3	−0.343 (±0.050)	—	—	−1.69 (±0.08)	14	0.813	0.286	47.8
18	Log EXC_3	−0.410 (±0.048)	−0.327 (±0.125)	—	−1.47 (±0.11)	14	0.888	0.232	39.9
19	Log EXC_3	—	—	−0.753 (±0.040)	—	14	0.967	0.368	350.0

Table VIII—Correlation Equations for Log DEA (Log Rate Constant of First Dealkylation) in Subjects 1–3

Equation	Dependent Variable	Log P_H	$f_{RR'}$	V_R	$C_\alpha H$	Intercept	n	r^2	s	F
20	Log DEA_1	0.280 (±0.031)	—	−0.0149 (±0.0032)	—	−1.20 (±0.09)	16	0.861	0.142	40.4
21	Log DEA_1	—	0.484 (±0.073)	−0.0152 (±0.0043)	—	−2.21 (±0.15)	16	0.770	0.183	21.8
22	Log DEA_1	—	0.390 (±0.067)	—	0.251 (±0.084)	−2.98 (±0.29)	16	0.729	0.198	17.5
23	Log DEA_2	0.371 (±0.065)	—	−0.0172 (±0.0068)	—	−1.06 (±0.20)	17	0.716	0.297	16.4
24	Log DEA_2	—	0.748 (±0.081)	−0.0213 (±0.0047)	—	−2.56 (±0.17)	17	0.868	0.203	42.8
25	Log DEA_2	—	0.606 (±0.086)	—	0.309 (±0.108)	−3.52 (±0.37)	17	0.793	0.254	24.8
26	Log DEA_3	0.299 (±0.039)	—	−0.249 (±0.0040)	—	−0.826 (±0.117)	16	0.832	0.176	32.3
27	Log DEA_3	—	0.500 (±0.093)	−0.0247 (±0.0054)	—	−1.88 (±0.19)	16	0.711	0.231	16.0
28	Log DEA_3	—	0.329 (±0.104)	—	0.331 (±0.130)	−2.92 (±0.44)	16	0.497	0.305	6.4

In contrast, the inclusion of the NH parameter markedly improves the statistics (Eqs. 12, 15, and 18). These equations confirm the conclusions obtained previously in that, for identical lipophilicities and when pKa is accounted for, tertiary amines undergo faster excretion than do secondary amines, which are excreted faster than primary amines. This structural influence has never been characterized, and no convincing physicochemical or biochemical explanation can be offered at present. Steric hindrance in the reabsorption process is a mere possibility.

Replacing log P_H with $f_{RR'}$ yields Eqs. 13, 16, and 19 in which the constant term is eliminated. The equations are less satisfactory than Eqs. 11, 14, and 17 due to larger standard deviations for reasons outlined earlier.

The best equations for log EXC_i are Eqs. 12, 15, and 18. Table III compares experimental and calculated log EXC_i values.

Rate Constant of First *N*-Dealkylation—For this biological response, 17 observations are available and consist of 14 compounds, three

of which bear two different N-substituents. From Table V, it is clear that log DEA is markedly dependent on lipophilicity, with log P_H and $f_{RR'}$ each accounting for ~50–60% of the variance (~30% for Subject 3). Equations based on log P_H or $f_{RR'}$ alone thus are below acceptable levels of significance and are not reported. The inclusion of quadratic terms or of NH did not improve the correlation.

Good levels of significance were obtained by including a second parameter that served as a descriptor of the N-substituent removed by dealkylation. This approach results in Eqs. 20–28 (Table VIII). Equations 20, 21, 23, 24, 26, and 27 indicate that the rate of the first dealkylation increases with increasing lipophilicity of the molecules (as assessed by log P_H or $f_{RR'}$) and with decreasing volume of the substituent that is split off. There is an apparent contradiction between these two trends, allowing an interesting insight into the molecular factors controlling N-dealkylation. The equations may mean that a high lipophilicity favors affinity to cytochrome P-450 and, hence, a fast reaction (2). On the other hand, the bulkier the substituent to be split off, the less favorable appears the initial C_α-hydroxylation ultimately leading to N-dealkylation.

Such an interpretation is strengthened by Eqs. 22, 25, and 28, which show that the rate of dealkylation increases with the number of hydrogen atoms on the α-carbon. In other words, increasing the steric bulk on the α-carbon being hydroxylated decreases the rate of N-dealkylation, suggesting that, in terms of the reaction mechanism, the C_α-hydroxylation by oxene transfer is the rate-limiting step in the overall N-dealkylation reaction.

Table VIII shows that the utility of the three sets of independent variables (log P_H and V_R, $f_{RR'}$ and V_R, and $f_{RR'}$ and $C_\alpha H$) varies from one subject to another. The set of log P_H and V_R yields the best correlations for Subjects 1 and 3 but not for Subject 2. This situation outlines the interest in quantitative structure–activity relationship studies of having a variety of parameters and descriptors available. The fourth possible set of variables, log P_H and $C_\alpha H$, does not yield significant equations, despite the orthogonality of the two variables (Table V).

Experimental log DEA_i values are compared in Table IV with the values calculated from the best equations in Table VIII.

CONCLUSION

The present study indicates that careful pharmacokinetic studies can yield biological data suitable for quantitative structure–activity relationship treatment and that following pharmacokinetic calculations with quantitative structure–activity relationship calculations can lead to new insights into, and a better understanding of, drug metabolism and disposition. This study also shows that the excretion of amphetamines decreases with increasing lipophilicity of the molecules and that, given the same lipophilicity, tertiary amines are excreted faster than secondary amines, which are excreted faster than primary amines. Also, the correlation equations indicate that the rate of N-dealkylation increases with increasing lipophilicity of the substrates (enhanced enzyme affinity) but decreases with increasing bulk of the N-substituent that is split off (steric hindrance of C_α-hydroxylation).

The quantitative nature of the correlations obtained will allow interesting comparisons with other series of drugs when data become available.

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Interactions of Cephalosporins and Penicillins with Nonpolar Octadecylsilyl Stationary Phase

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Abstract □ The capacity factors of several penicillins and cephalosporins, as well as those of 7-aminocephalosporanic acid, 6-aminopenicillanic acid, and 7-aminodeacetoxycephalosporanic acid, were determined at pH 2.5–7.5 with different methanol concentrations in the mobile phase. The influence of ionic strength on activity factors also was studied. Some theoretical equations providing a quantitative description of the influence of the mobile phase pH on the retention of penicillins and cephalosporins by an octadecylsilyl stationary phase were established. The analysis of experimental data by a nonlinear least-squares fit to theoretically deduced equations permitted determination of the capacity factors of anionic, cationic, zwitterion, and undissociated forms of the substances studied.

Keyphrases □ Cephalosporins—interactions with a nonpolar octadecylsilyl stationary phase □ Penicillins—interactions with a nonpolar octadecylsilyl stationary phase □ Capacity factors—cephalosporins and penicillins, interactions with a nonpolar octadecylsilyl stationary phase □ Antibiotics—cephalosporins and penicillins, interactions with a nonpolar octadecylsilyl stationary phase, capacity factors

Penicillins and cephalosporins constitute a large family of antibiotics of generalized use and similar structure. All of these compounds have at least one carboxylic group, and some possess one or more amino groups. Therefore, depending on the medium, they can be in undissociated, anionic, cationic, or zwitterion form.

There have been several studies of nonpolar stationary phases for the separation of certain cephalosporins and penicillins (1–4). However, a more systematic study of the influence of the ionization of penicillins and cephalosporins on interactions with nonpolar octadecylsilyl stationary phases was desired to elucidate the factors in the chro-

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