tion coefficient becomes asymptotic at high concentrations of the ion-pairing agent. The assay for methylene blue in urine and blood (2) depends upon such partitioning in the presence of high concentrations of sodium chloride.

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Pharmacokinetics of Highly Ionized Drugs III: Methylene Blue—Blood Levels in the Dog and Tissue Levels in the Rat following Intravenous Administration

ANTHONY R. DiSANTO* and JOHN G. WAGNER▲

Abstract □ Plasma concentrations following rapid intravenous injection of 2-, 5-, 7.5-, 10-, and 15-mg./kg. doses of methylene blue in a dog were obtained. The single-dose data were fit to both a nonlinear heterogeneous one-compartment open model with binding to one type of tissue and the classical linear two-compartment open model. Fitting to the nonlinear model showed *no* systematic trends in the estimated parameters in relation to dose. Fitting of the concentration data to the classical linear two-compartment open model *did show* systematic trends in the estimated parameters in relation to dose. Rats were injected intravenously with 2-, 5-, 7.5-, 10-, 15-, and 25-mg./kg. doses of methylene blue and were then decapitated 3 min. later. The lungs, liver, kidneys, and heart were removed and assayed. An average of 29.8% of the dose (range 25.2–35.8%) was recovered in those four tissues, indicating very rapid uptake and extensive uptake of methylene blue by tissues. A plot of the average amount taken up by those tissues against the milligrams per kilogram dose was fit by the equation appropriate to the nonlinear model.

Keyphrases □ Methylene blue—dog plasma and rat tissue concentrations after intravenous administration, pharmacokinetics □ Pharmacokinetics of highly ionized drugs—methylene blue, dogs, rats □ Plasma levels, methylene blue—intravenous administration, dogs □ Tissue levels, methylene blue—intravenous administration, rats

A generalized nonlinear pharmacokinetic model was elaborated by DiSanto and Wagner and published by Wagner (1). The relationship of this model to nonlinear models of other investigators was discussed by DiSanto and Wagner (2). The simplest specific case of the generalized model is the heterogeneous one-compartment open model with binding to one type of tissue. All of the equations appropriate to this model were given by Wagner (1) and some of them were given by DiSanto and Wagner (2). The integrated equation for the plasma concentration as a function of time, Eq. 4 of this report, is analogous to, but different than, equations derived by Krüger-Thiemer (3, 4) for nonlinear plasma protein binding of drugs. The purposes of this report are:

1. To list plasma concentrations measured after the intravenous administration of 2-, 5-, 7.5-, 10-, and 15-mg./kg. doses of methylene blue to a male beagle dog.
2. To list tissue levels in heart, lungs, liver, and kidneys measured at 3 min. after the rapid intravenous injection of 2-, 5-, 7.5-, 10-, 15-, and 25-mg./kg. doses of methylene blue to the rat.
3. To evaluate these data by both the classical linear two-compartment open model and the nonlinear heterogeneous one-compartment open model with binding to one type of tissue.

EXPERIMENTAL

Materials—A solution of methylene blue[1] in sterile water for injection was prepared, transferred to 10-ml. vials, and autoclaved. Two vials were assayed and the concentration was calculated from the Beer's law slope of methylene blue in water. The intravenous solution assayed 2% w/v methylene blue. This preparation was used in all of the intravenous administrations of methylene blue to the dog.

[1] Fisher Scientific.

Table I—Whole Blood Concentrations Measured following Intravenous Administration to a Male Dog

2 mg./kg. (22.4 mg.)		5 mg./kg. (56.0 mg.)		7.5 mg./kg. (84.0 mg.)	
Time, hr.	Concentration, mcg./ml.	Time, hr.	Concentration, mcg./ml.	Time, hr.	Concentration, mcg./ml.
0.046	0.941	0.054	2.60	0.058	7.07
0.175	0.365	0.165	0.715	0.184	2.80
0.325	0.275	0.337	0.438	0.330	1.68
0.493	0.199	0.497	0.403	0.492	1.32
0.997	0.124	1.01	0.230	0.988	0.677
2.20	0.0640	2.03	0.130	1.995	0.211
3.11	0.0424	4.07	0.071	3.999	0.117
4.22	0.0310	5.05	0.052	4.998	0.093
—	—	6.005	0.034	—	—

10 mg./kg. (112.0 mg.)		15 mg./kg. (168.0 mg.)		Predose (112–161 mg.)	
Time, hr.	Concentration, mcg./ml.	Time, hr.	Concentration, mcg./ml.	Time, hr.	Concentration, mcg./ml.
0.079	21.68	0.046	31.2	0.0	0.217
0.273	7.22	0.163	15.01	0.054	5.3
0.320	2.18	0.323	2.45	0.161	1.06
0.567	0.965	0.491	1.44	0.331	0.412
1.013	0.471	1.01	0.396	0.496	0.296
2.030	0.163	2.01	0.238	0.996	0.270
4.020	0.141	4.01	0.189	1.992	0.201
6.220	0.077	4.99	0.152	3.975	0.167
—	—	6.03	0.122	5.005	0.152
—	—	7.25	0.085	5.960	0.123

Dog Studies[2]—The dog was fasted the night before each administration and for the duration of each experiment. Water was allowed *ad libitum*. The dog was weighed prior to each experiment and the dose was calculated on a milligrams per kilogram basis. Two intravenous catheters were inserted, one in the right front leg vein and the other in the left hind leg. The drug was administered in the right front leg and samples were taken from the hind leg. A threeway stopcock arrangement was used during injection to allow flushing of the syringe with normal saline after the methylene blue was administered. After each blood sample was taken, 2–3 ml. of normal saline was pushed through the intercath to keep it patent. The time and volume of blood were recorded as the samples were drawn. A timer[3] which read to one-hundredth of a minute was used in the studies. The sampling times are listed in Table I. The blood was assayed during the 2-hr. sampling intervals, and sampling was usually stopped when the blood concentration was approaching the assay sensitivity. In some studies it was not possible or it was impractical to draw more blood from the dog. Variations from the sampling schedule occurred when the dog was uncooperative or the intercath was not patent. Variations in the sampling times from study to study did not affect the pharmacokinetic analysis of the data obtained from the intravenous experiments.

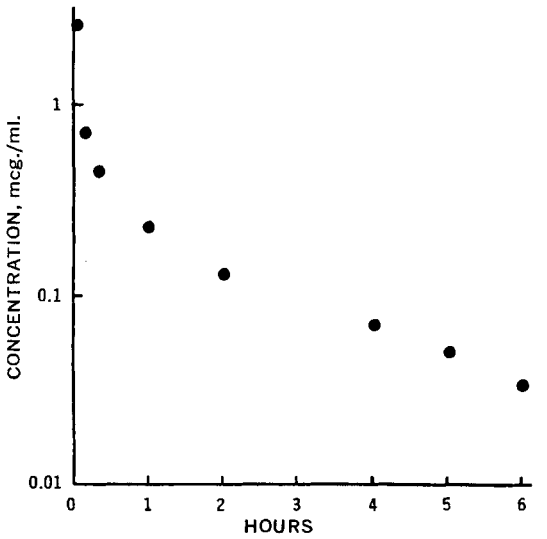

Figure 1—*Semilogarithmic blood concentration–time relationship of methylene blue in the dog following an intravenous dose of 5 mg./kg.*

The dog was administered five different single doses of methylene blue, allowing at least 2–3 weeks between experiments. The single doses administered were 2, 5, 7.5, 10, and 15 mg./kg. A "predose" study was also conducted in the same dog. In this case the dog was administered a 10-mg./kg. dose of methylene blue intravenously, followed 1 hr. later by a 5-mg./kg. i.v. dose of methylene blue. The sampling times recorded in Table I are such that the time of administration of the 5-mg./kg. dose is considered zero time (*i.e.*, 1 hr. after the 10-mg./kg. dose). The zero-hour blood sample was taken just prior to the 5-mg./kg. dose.

Whole blood was assayed by the extraction–spectrophotometric method of DiSanto and Wagner (5). This assay measures both unchanged methylene blue and the metabolite leucomethylene blue. However, the reduction of methylene blue to leucomethylene blue and the oxidation of leucomethylene blue to methylene blue are essentially instantaneous. Hence, kinetically, measuring both in whole blood and tissue is analogous to the usual assay for only unchanged drug.

Table II—Parameters Estimated for the Two-Compartment Open Model by Nonlinear Least-Squares Fitting of Whole Blood Concentrations (Weighted According to Their Reciprocals) and Measures of Fit

Parameter	Dose, mg./kg. 2	5	7.5	10	15
k_{12}, hr.$^{-1}$	3.49[a] (1.29)[b]	7.10 (1.27)	2.12 (1.81)	1.73 (1.69)	2.09 (0.896)
k_{21}, hr.$^{-1}$	1.15 (0.232)	1.02 (0.151)	0.410 (0.295)	0.280 (0.206)	0.289 (0.131)
k_{el}, hr.$^{-1}$	1.94 (0.497)	3.43 (0.649)	2.61 (1.69)	6.36 (1.72)	6.32 (0.862)
V_1, l.	20.2 (2.81)	11.8 (1.94)	10.0 (1.08)	2.73 (0.549)	3.53 (0.319)
r^2	0.986	0.990	0.979	0.985	0.992
Corr.	0.998	0.993	0.983	0.991	0.995

[a] Estimated value of parameter. [b] Number in parentheses is the standard deviation of the estimated parameter.

[2] An 11.5-kg. male beagle dog, obtained from Tri Co Animal Research Laboratories, Kalamazoo, Mich., was used in all intravenous dog studies.

[3] Precision Scientific.

Table III—Estimated and Derived Parameters of Dog Intravenous Data Fit to One-Compartment Open Model with One Type of Tissue Binding (Fitted by NONLIN with Reciprocal Weighting to Eq. 4)

Dose, mg./kg.	Estimated Parameters: A, mcg./ml.	B, mcg./ml.	K, hr.$^{-1}$	C_0, mcg./ml.	Derived Parameters: V[a], l./kg.	A'[b], mg./kg.	K_{eq}[c]	Measures of Fit: r^2	Corr.
2	12.9 (8.78)[d]	0.0355 (0.026)	15.4 (1.05)	1.57 (0.064)	0.141	1.82	200.0	0.998	0.998
5	16.2 (24.8)	0.0276 (0.046)	10.5 (1.29)	4.13 (0.638)	0.248	4.00	147.0	0.986	0.991
7.5	14.5 (14.6)	0.103 (0.118)	5.70 (0.679)	9.04 (1.13)	0.320	6.89	30.3	0.989	0.991
10	12.9 (19.5)	0.0582 (0.094)	8.11 (1.13)	41.6 (8.15)	0.184	2.41	91.7	0.985	0.990
15	21.4 (50.0)	0.0426 (0.090)	8.20 (0.633)	47.08 (19.0)	0.219	4.68	50.5	0.992	0.995
Average	15.6	0.053	9.53		0.222	3.96	104.0		

[a] $V = \frac{D}{T_0 + C_0}$, where $T_0 = \frac{AC_0}{B + C_0}$. [b] $A' = A \cdot V$. [c] $K_{eq} = 1/B \cdot V$. [d] Standard deviation of estimated parameter.

Table IV—Volumes, Elimination Rate Constants, and Plasma Clearances

Dose, mg./kg.	Classical Linear Two-Compartment Open-Model Analysis: V_1, l./kg.	k_{el}, hr.$^{-1}$	$V_1 \cdot k_{el}$, l./kg./hr.	Nonlinear One Fluid–One Tissue Model Analysis: V, l./kg.	K, hr.$^{-1}$	$V \cdot K$, l./kg./hr.
2	1.80	1.94	3.49	0.141	15.4	2.17
5	1.13	3.43	3.88	0.248	10.5	2.60
7.5	0.893	2.61	2.33	0.320	5.70	1.82
10	0.244	6.36	1.55	0.184	8.11	1.49
15	0.315	6.32	1.99	0.219	8.20	1.80
Average	0.876	4.13	2.65	0.222	9.58	1.98
SD	0.639	2.08	0.996	0.0676	3.67	0.424
CV, %	72.9	50.4	37.6	30.4	38.3	21.5

Rat Studies[4]—The solution of methylene blue used in these studies was the same as in the intravenous dog studies. The rats were fasted overnight prior to each study and were briefly anesthetized with ether and weighed. A 45-mg./kg. dose of sodium pentobarbital[5] was administered intraperitoneally. One-half a milliliter of a 40-mg./ml. solution was administered initially, 10–15 min. was allowed to pass, and then the remainder of the dose was given. A dose of 0.8 mg. of atropine sulfate was then given subcutaneously to help prevent aspiration of fluids. Methylene blue was then injected intravenously into the penis vein, and the rat was decapitated with a guillotine 3 min. later. The blood was allowed to drain into a beaker lightly coated with acid-citrated dextrose and assayed in a similar manner as the whole dog blood. The lungs, liver, kidneys, and heart were removed and assayed as described by DiSanto and Wagner (5). The six doses of methylene blue administered were 2, 5, 7.5, 10, 15, and 25 mg./kg. of body weight.

RESULTS AND DISCUSSION

Table I lists the observed whole blood concentrations for the six studies performed in the same male dog. Figure 1 is a semilogarithmic plot of the 5-mg./kg. dose data, and Fig. 2 is a semilogarithmic plot of the 15-mg./kg. dose data. These are representative of similar plots of the data obtained following the other doses. The relationship is apparently biexponential; hence, one could initially assume that Teorell's (6) classical linear two-compartment open model applies to these data. The appropriate equations for bolus intravenous injection and this model are:

$$C_1 = \frac{D}{V_1(\alpha - \beta)}[(k_{21} - \beta)e^{-\beta t} - (k_{21} - \alpha)e^{-\alpha t}] \quad \text{(Eq. 1)}$$

where:

$$\alpha + \beta = k_{12} + k_{21} + k_{el} \quad \text{(Eq. 2)}$$

and:

$$\alpha \cdot \beta = k_{21}k_{el} \quad \text{(Eq. 3)}$$

Preliminary estimates of the parameters were obtained by the feathering or back-projection technique using semilogarithmic graph paper. Data from all five single intravenous doses of methylene blue administered to the dog were fitted by the method of least squares with an iterative digital computer program and an IBM 360/65 digital computer to conform to Eq. 1. The graphical estimates of the parameters were used as starting values, and the concentrations were assigned reciprocal weights. The least-squares estimates of the parameters k_{12}, k_{21}, k_{el}, and V_1, obtained by this procedure, are listed in Table II. The data fit well to the two-compartment model, as indicated by the high coefficients of determination and correlation coefficients for the regression of predicted or observed C_1 values. Table II, however, reveals that although the data were fitted well, there are systematic trends in the estimated parameters in

Table V—Tissue Uptake of Methylene Blue after Intravenous Administration to the Rat

Tissue	Amount Methylene Blue Bound, mcg./g. Tissue: Dose, mg./kg. 2	5	7.5	10	15	25
Heart	15.8	40.7	45.5	46.8	97.9	114.0
Lung	9.56	31.0	28.5	23.5	49.1	80.9
Liver	13.7	45.9	37.2	41.1	107.0	77.6
Kidney	18.2	52.3	78.6	93.2	124.0	386.0
	Percent Dose in Four Tissues Assayed: 32.0	35.8	30.5	25.3	30.2	25.2

[4] Adult male Sprague-Dawley rats, weighing between 300 and 400 g., were obtained from the University of Michigan Animal Research Facility and were used in all experiments.
[5] Nembutal Sodium, Abbott Laboratories, Chicago, Ill.

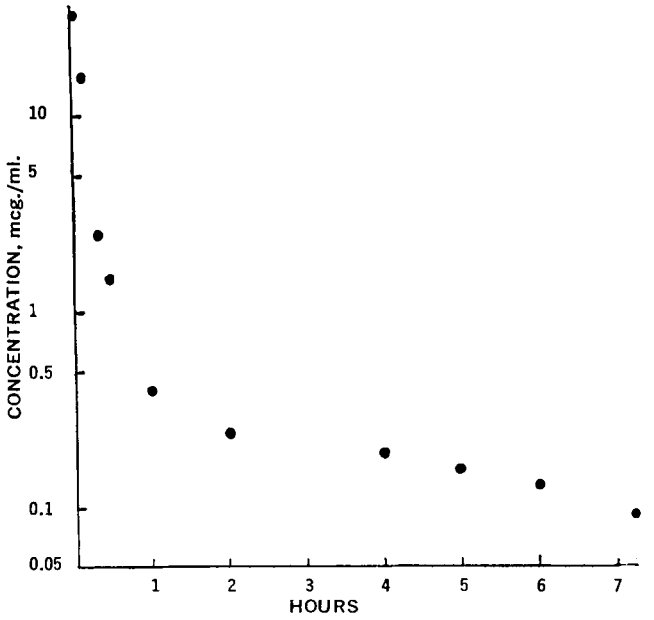

Figure 2—*Semilogarithmic blood concentration–time relationship of methylene blue in dog following an intravenous dose of 15 mg./kg.*

relation to the dose. Note that as the dose increases, V_1 and k_{21} decrease, while k_{el} increases with increasing dose. A trend also occurs with $t_{1/2} = (\ln 2)/\beta$. Note that β decreases with increasing dose, or the half-life increases with increasing dose. Similar trends were also noted for k_{el} and β in the simulations performed by DiSanto and Wagner (2).

The same five sets of data were also fitted by the method of least squares using an iterative procedure to Eq. 4, which is appropriate to the heterogeneous one-compartment open model with binding to one type of tissue:

$$t = \frac{1}{K}\left[\left(1 + \frac{A}{B}\right)\ln\left(\frac{C_0}{C}\right) + \frac{A}{B}\ln\left\{\frac{B + C}{B + C_0}\right\} + A\left\{\frac{C - C_0}{(B + C)(B + C_0)}\right\}\right] \quad \text{(Eq. 4)}$$

As with the two-compartment open-model analysis, excellent fits of all five sets of data were obtained. However, with this model there were no systematic trends in the estimated or derived parameters, as seen from the data listed in Table III.

The volumes, model elimination rate constants, and plasma clearances ($V_1 \cdot k_{el}$ and VK) obtained by both models are given in Table IV. These data show that the variability of each of those parameters, as evidenced by the coefficients of variation, were considerably greater for the linear two-compartment analysis than for the nonlinear analysis.

The average volume of distribution, expressed as fraction of body weight obtained by the individual fitting of the five sets of blood concentrations to the nonlinear model, was 0.222 or 22.2% body weight. The average volume of distribution obtained from 10 dogs of varying weight, calculated by Sapirstein *et al.* (7), using mannitol and creatinine was 20.3 and 19.7% body weight, respectively. These drugs are not tissue bound, and the volumes determined by their use represent a physiological fluid volume. The volume of distribution obtained from the nonlinear analysis of the highly tissue-bound methylene blue is quite similar to that obtained by Sapirstein *et al.* (7). It appears, therefore, that the volume of distribution obtained by this nonlinear model may indeed have a physiological significance. In contrast, the average volume of the inner (plasma) compartment by two-compartment analysis was 87.6% of body weight and one value was 180% of body weight.

In the predose study, the blood samples taken 3 min. after the 5-mg./kg. dose assayed 5.3 mcg./ml., whereas the corresponding value was 2.6 mcg./ml. at the same time after the single 5-mg./kg. dose. The 0.217-mcg./ml. value at zero time in the predose study obviously cannot explain this difference. But the tissues that were loaded with the drug by the loading dose can explain the difference.

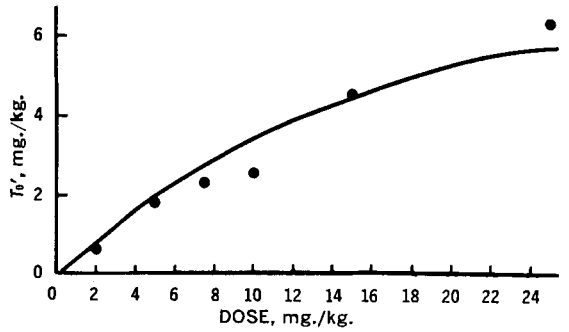

Figure 3—*Initial amount of drug bound* (T_0') versus *dose* (D) *plot of various intravenous doses of methylene blue to the rat. Line indicates predicted values obtained from fitting to Eq. 5, and dots* (●) *are observed values.*

Qualitatively, the predose study supported the nonlinear binding model.

The purposes of the rat experiments were to show extremely rapid uptake of methylene blue by tissue and to obtain data on the amount bound as a function of dose. Table V lists the results of these studies. On opening the body cavity of the rat after sacrificing, there was no observable blue coloration of any tissue. On exposure to the air, several organs became markedly blue in color. This emphasizes the rapid reduction of methylene blue to leucomethylene blue by red blood cells and possibly other tissues and its equally rapid reoxidation to methylene blue.

It is realized that a certain percentage of the tissue weight is blood, and as such a correction for the amount of methylene blue in this blood might have been made. It was found that the amount of methylene blue in the blood in the tissues was negligible compared to the amount of methylene blue in the tissues studied. The blood volume of the rat liver and heart was reported as 18–20% (8, 9). Using the value of 20% as the blood volume for each of the four organs studied did not even account for 1% of the amount of methylene blue found in each tissue. The correction for the blood content in the tissue was, therefore, neglected.

The four organs in this study accounted for an average of 29.8% of the administered dose of methylene blue, even though the rats were killed 3 min. postinjection.

For the nonlinear model, the relationship between the initial amount of drug bound, T_0', and the dose, D, for the one-compartment open model with binding to one type of tissue is given by Eq. 5:

$$T_0' = \tfrac{1}{2}\left[(D + K_d \times A') - \sqrt{(D + K_d + A')^2 - 4A'D}\right] \quad \text{(Eq. 5)}$$

where T_0' is the initial amount of drug taken up by tissue after administration of the intravenous dose, D is the dose in milligrams per kilogram, K_d is the dissociation constant of the tissue–drug complex, and A' is the maximum amount of drug (milligrams per kilogram) that can be taken up by tissue. In applying this equation to the rat tissue data, the assumptions are made that the amount in the tissues at 3 min. postinjection is the same as immediately after injection and that the different tissues assayed may be pooled and considered as one type of tissue so far as pharmacokinetic analysis is concerned.

The rat tissue data were fitted to this equation using the program NONLIN[6]. An average T_0' was obtained from the four tissues assayed. An initial estimate of A' was obtained as the approximate asymptote of a T_0' *versus* D plot, and K_d was estimated from Eq. 6:

$$D = T_0' - K_d\left[1 + \frac{A'}{(T_0' - A')}\right] \quad \text{(Eq. 6)}$$

The result of this fitting is shown in Fig. 3.

These rat tissue studies clearly illustrate rapid uptake of methylene blue by tissue and also lend credibility to the assignment of the

[6] Kindly supplied by Dr. C. M. Metzler, The Upjohn Co., Kalamazoo, Mich.

nonlinear heterogeneous one-compartment—one type of tissue—model to the dog intravenous studies.

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Use of Thermal Gravimetric Analysis in Sorption Studies II: Evaluation of Diffusivity and Solubility of a Series of Aliphatic Alcohols in Polyurethan

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Abstract □ A thermogravimetric analysis method was used to evaluate the diffusion and solubility of a series of aliphatic alcohols in a specific polyurethan film at several different temperatures. The diffusion coefficients were calculated from desorption curves by the use of a specific equation applied to the early stages of desorption. In general, the diffusion coefficients of the straight-chain alcohols increased with temperature and decreased with molecular weights. The branched-chain alcohols had diffusion coefficients lower than the nonbranched isomers. Activation energies of diffusion were also calculated and fell into the range of 9.16–14.5 kcal./mole. By knowing the diffusion and the solubility coefficients, the permeability constants were estimated.

Keyphrases □ Alcohols, aliphatic—diffusivity and solubility in polyurethan films, thermogravimetric analysis □ Polyurethan films—diffusivity and solubility of aliphatic alcohols, thermogravimetric analysis □ Diffusion coefficients of aliphatic alcohols—polyurethan films, thermogravimetric analysis □ Thermogravimetric analysis—diffusivity and solubility of aliphatic alcohols in polyurethan films

Greater attention is now being paid to the possible interaction of drugs with various plastics and elastomers used for packaging of drugs or as various types of collection and administration devices. Reduction of potency of the drug or a preservative in the product due to an interaction with the plastic can pose from minor to serious consequences to the patient. A previous communication (1) from these laboratories reported on the use of thermogravimetric analysis (TGA) as a rapid and simple means of studying drug–plastic interactions. In that study a group of liquid compounds were first placed in contact with a specific plastic (nylon 66) until equilibrium was attained. The material was then placed into the TGA instrument, and the desorption was followed in a dynamic manner by increasing the temperature at a constant rate. The resultant thermogram then permitted an evaluation of the equilibrium sorption concentration and the energy of activation of desorption which, in turn, permitted a qualitative insight as to the role the structure of the compound played in the sorption process.

The present report extends these TGA studies on the interaction of a series of aliphatic alcohols with a specific plastic, polyurethan. Desorption experiments permitted the calculation of the diffusion coefficients of these alcohols and the activation energies of diffusion. The equilibrium sorption concentration of each compound at different temperatures was also evaluated.

EXPERIMENTAL

Materials—The following eight alcohols were used in this study: methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-methyl-1-propanol, 1-pentanol, and 1-octanol. All of these compounds were of reagent grade or of the highest purity obtainable commercially. They were used as such without further purification. Table I lists the alcohols and summarizes some physical properties for each compound.