

Use of Thermal Gravimetric Analysis in Sorption Studies I: Interaction of Selected Liquid Compounds with Nylon

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Abstract □ Thirty-nine liquid compounds were studied as to their sorption by nylon. Each liquid was kept in contact with test samples of nylon until equilibrium was established, and then the amount of compound sorbed was determined in a thermogravimetric analysis instrument. The same instrument was then used to desorb the compound from the nylon at a specified rate of heating. The resulting thermogram permitted the evaluation of the activation energy of desorption. Twenty compounds were found to be significantly sorbed by nylon, while the remaining compounds were not significantly sorbed. It was apparent that compounds having hydrogen-bonding potential would interact with nylon in most instances. Several compounds not possessing hydrogen-bonding properties were also sorbed but to a much lesser extent. The size of the molecule in a homologous series also played a part in the extent of sorption and in the energy requirement for sorption. Thermal gravimetric analysis appears to be a practical method for conducting sorption studies when large numbers of compounds are to be studied or screened for a packaging application in a polymeric material.

Keyphrases □ Sorption equilibria—liquids sorbed by nylon □ Nylon—liquid sorption equilibrium—thermal gravimetric analysis □ Thermal gravimetric analysis—liquid—nylon sorption □ Activation energy, desorption—liquids from nylon □ Containers, plastic—liquids—nylon sorption

The packaging of pharmaceutical products in plastic containers and in various types of packaging devices requires that little or no interaction takes place between the component in the product and the plastic. Such drug-plastic interaction can lead to a reduction in the potency of the product, negating its value. One method of ascertaining if potential drug-plastic interactions will occur is to undertake sorption studies at one or more isothermal conditions with the test compound and the specific plastic. When properly conducted, the equilibrium sorption studies can lead to data which can then be treated on a thermodynamic basis. Studies of this type have appeared in the literature in recent years (1-5).

While sorption studies at isothermal conditions are excellent for generating both kinetic and thermody-

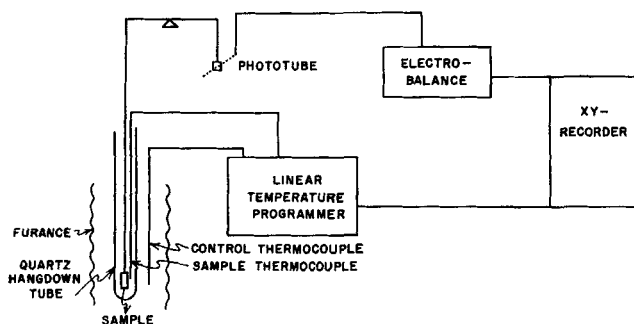


Figure 1—Schematic diagram of TGA instrument for desorption studies.

amic data, they are generally quite time consuming when a large number of compounds are to be studied with a specific polymer. For this reason, attention was directed toward the use of thermogravimetric analysis (TGA) in which one experiment could be utilized to determine the equilibrium sorption of the test compound as well as the activation energy of desorption. This latter value can also be considered as approximating the heat of desorption which, in turn, should be equal to the magnitude heat of sorption. In the report presented here, 39 compounds as liquids, representing a broad spectrum of molecular properties and functional groups, were studied as to their equilibrium sorption with nylon.

EXPERIMENTAL

Materials and Equipment—The compounds used in the study were either reagent grade or of a similar purity and were used as such. Nylon-6,6¹ was used as the film, having an average thickness of 0.013 cm. (0.005 in.).

A schematic diagram of the TGA instrument² is shown in Fig. 1. A straight nichrome wire, 0.1 mm. diameter and 33 cm. long, was used to load the sample on the balance beam. Both the sample weight change and temperature could be recorded simultaneously.

Preparation of Sample—Nylon film was soaked in 95% (v/v) alcohol for a period of 24 hr. and then rinsed with distilled water a total of six times to remove contaminants. After drying for 12 hr. at 50°, the sample was placed into a desiccator until needed for a sorption experiment. Prior to an experiment, the film was removed from the desiccator and cut into sections measuring 0.63 × 1.27 cm. (0.25 × 0.5 in.)³. One section (or sample) was then placed into the TGA instrument and heated to 120° at a programmed heating rate of 5°/min. to remove any sorbed water from the sample. Preliminary experiments indicated that this treatment would be adequate in removing sorbed water from the film.

At the end of the heating cycle, the exact weight of the test sample was recorded at 25°, and the sample was then immersed into 10 ml. of one of the test liquids previously placed into an all-glass conical flask (25-ml. size). After the flask was sealed with a ground-glass stopper, it was stored at a temperature of 25 ± 0.5° in a constant-temperature room for 1 week or until it was apparent that equilibrium was obtained. The test sample was then removed by blotting the film with tissue paper. Immediately, the sample was introduced into the TGA, the sample weight was recorded, and a thermogram was determined.

TGA Procedure for Desorption Studies—In any desorption run for the liquids in this study, the electrobalance was set at a sensitivity of 0.01 mg. and recorded on a 1-mv. instrument. Temperature was programmed to increase at a rate of 5°/min. To prevent chemical oxidation of the nylon and to sweep out volatile substances not sorbed, nitrogen gas was passed through the heating chamber at a rate of 0.1 l./min. The weight loss of the sample was recorded in the temperature range from 25 to 200°. In this temperature range, nylon is not thermally degraded. It was ascertained that the in-

¹ Polypenco 101, Polymer Corporation of Pennsylvania, Reading, Pa.

² The TGA instrument consisted of the following: (a) Fisher model 100 TGA System, Fisher Scientific Co., Pittsburgh, Pa.; (b) Cahn RG electrobalance, Cahn Instrument Co., Paramount, Calif.; and (c) Servo/Riter II potentiometric XY recorder, Texas Instrument Co., Houston, Tex.

³ Approximately 20 mg.

Table I—Compounds Studied in Sorption Experiments with Nylon^a

Compounds Not Significantly Sorbed	Compounds Significantly Sorbed
Carbon tetrachloride	Water
Ethylene dichloride	Methanol
Ethyl bromide	Ethanol
Methyl benzoate	Propanol
Aniline	Butanol
Anisole	Pentanol
Benzonitrile	Acetic acid
Ethynyl benzene	Chloroform
Chlorobenzene	Ethylene glycol
Phenyl isothiocyanate	2-Chloroethanol
<i>o</i> -Nitroanisole	Ethyl iodide
Methyl salicylate	Acetone
2-Hydroxyacetophenone	Methyl acetate
Benzaldehyde	Phenol
<i>p</i> -Isopropylbenzaldehyde	Benzyl alcohol
<i>p</i> -Tolualdehyde	Benzyl chloride
Anisoaldehyde	Benzaldoxime
<i>o</i> -Chlorobenzaldehyde	Benzene
<i>trans</i> -Cinnamaldehyde	Toluene
	Acetophenone

^a The weight of sample used in the sorption studies was approximately 20 mg. Since the instrument used was accurate to ± 1.0 mg., "significant sorption" occurred when the amount of compound sorbed was greater than 0.2 mg.

strument as used in this study produced an error of less than $\pm 1\%$ in the recording of weights.

Treatment of Data—Numerous methods have been proposed for deriving kinetic parameters from TGA thermograms. Quantitative aspects of this subject dealing with degradation of polymers were presented by Madorsky (6), Doyle (7) and Freeman and Carroll (8) presented equations which permit the calculations of activation energies of degradation and orders of reaction. More recently, Broido (9) reported a simplified method for evaluating the activation energy of degradation of polymers. Broido's method (9) was found to be more sensitive to small weight changes than previous methods. Even though these aforementioned authors used their respective expressions for evaluating the energy requirement for degradation of polymers, the same expressions should also be applicable for approximating the energy requirement for binding a molecule to a polymer. In this case, the activation energy of desorption may be considered as approaching in magnitude the thermodynamic constant referred to as the "heat of sorption."

Preliminary treatments of thermogram data established that Broido's method (9) was the most suitable for calculating the activation energy. His expression may be written as:

$$\ln \ln (1/Y) = - \frac{E}{RT} + \text{constant} \quad (\text{Eq. 1})$$

where Y is further defined as:

$$Y = \frac{W_t - W_\infty}{W_0 - W_\infty} \quad (\text{Eq. 2})$$

and E , R , and T are the activation energy of desorption, the universal gas constant, and the absolute temperature, respectively. The terms in Eq. 2 are further defined as: W_t = weight at time t ; W_0 = weight at beginning of experiment (start of desorption); and W_∞ = weight at end of experiment (end of desorption).

A plot of $\ln \ln (1/Y)$ versus $1/T$ yields a linear relationship from which E can be calculated by knowing the slope of the line.

RESULTS AND DISCUSSION

Equilibrium sorption experiments were run on 39 liquid compounds at 25°, and the final weights of sorption were determined in the TGA apparatus prior to conducting the desorption experiments. Since the accuracy of the method used was $\pm 1\%$ or less, equilibrium sorption weights of less than 0.2 mg. (for 20-mg. sample of nylon) were considered as "not significantly sorbed." Of the 39 compounds studied, 20 compounds showed significant sorption. Table I lists both the compounds not sorbed and those which

Table II—Equilibrium Sorption Concentrations of Compounds Sorbed by Nylon

Compound	Milligrams per Gram	Millimoles per Gram
Water	79.2	4.4
Methanol	83.3	2.6
Ethanol	96.7	2.1
Propanol	85.9	1.43
Butanol	24.4	0.33
Pentanol	14.1	0.16
Acetic acid	252.2	4.2
Chloroform	182.7	1.53
Ethylene glycol	105.5	1.7
2-Chloroethanol	262.5	3.3
Ethyl iodide	62.4	0.4
Acetone	21.5	0.37
Methyl acetate	21.1	0.27
Phenol ^a	—	—
Benzyl alcohol	205.4	1.9
Benzyl chloride	60.8	0.48
Benzaldoxime	70.3	0.58
Benzene	10.1	0.13
Toluene	12.0	0.13
Acetophenone	132.5	0.11

^a Phenol dissolves the nylon.

were sorbed by nylon. The weights of compounds sorbed at equilibrium are shown in Table II.

Activation energies of desorption for the compounds studied are listed in Table III. An example of a Broido (9) plot for benzyl alcohol is depicted in Fig. 2, from which the activation energy was calculated. For each compound, two thermograms were prepared and the average slope was then used in the calculation of the activation energy. All of the compounds, when plotted as shown in Fig. 2, were linear, with all of the points falling on the line. Table III also contains the heats of vaporization for each compound.

A knowledge of the structures of the compounds (Table I), the amount of sorption (Table II), the activation energies of desorption (Table III), and the heats of vaporization (Table III) can help to present some tentative suggestions as to the mechanism of interaction of the compounds studied with nylon.

Nylon has three polar sites in its structure where binding may occur with various types of molecules: (a) an end amino group, (b) an end carboxylic group, and (c) repeating amide groups in the polymer chain. By far the most frequent groups are the amide linkages, thereby implying that this site is perhaps the most significant for interactions. Previous reports suggested that for unionized molecules having acidic hydrogens or hydrogens capable of forming hydrogen bonds, an interaction of the molecule with the carbonyl

Table III—Activation Energies of Desorption and Heats of Vaporization for Compounds Sorbed by Nylon

Compounds	Energy of Activation, kcal./mole	Heat of Vaporization, kcal./mole
Water	8.7	9.7
Methanol	8.6	8.4
Ethanol	8.1	9.4
Propanol	9.0	9.9
Butanol	10.3	10.5
Pentanol	12.9	10.7
Acetic acid	5.2	5.8
Chloroform	7.2	6.96
Ethylene glycol	7.3	11.8
2-Chloroethanol	5.1	9.8
Ethyl iodide	9.0	7.1
Acetone	7.0	7.65
Methyl acetate	9.6	7.25
Phenol ^a	—	—
Benzyl alcohol	6.3	12.1
Benzyl chloride	8.1	— ^b
Benzaldoxime	8.6	— ^b
Benzene	8.1	7.35
Toluene	12.5	8.0
Acetophenone	11.5	7.7

^a Phenol dissolves nylon. ^b Reported value not found.

group in the amide structure in nylon can take place through a hydrogen-bond formation (10).

The derivation of activation energy of desorption, which is achieved by the method described in this paper, permits the consideration of the possible mechanisms of interaction between the compound and the substrate. It is recognized, of course, that thermal measurements by themselves do not offer sufficiently conclusive evidence in this regard. An analysis of the nature of the bonding interaction, however, is possible, at least as an initial step, leading to the design of adequate experiments by suitable techniques to pursue mechanistic details in greater depth if required.

An examination of the compounds not significantly sorbed (Table I) shows that only two of the series have hydrogens capable of forming hydrogen bonds with nylon. These are methyl salicylate and 2-hydroxyacetophenone. Their lack of significant sorption with nylon may be due to the intrahydrogen bond formation preventing the OH groups from interacting with nylon.

As Table I reveals, 20 of the 39 compounds studied were sorbed by nylon. Of these 20 compounds, 12 have OH groups capable of hydrogen-bond formation; therefore, it appears reasonable to assume that these compounds will hydrogen bond with the amide linkages in the nylon. Since hydrogen in chloroform is sufficiently positive, the sorption of this compound may also take place through a hydrogen bond. Acetone, methyl acetate, and acetophenone have carbonyl oxygens and thus can act as sites of interaction with other molecules possessing acidic hydrogens. This suggests, but does not prove, that sorption of these three compounds may take place *via* the amide hydrogen of nylon interacting with the carbonyl oxygen of the compounds.

Sorption through hydrogen bonding cannot explain the interaction of four compounds (ethyl iodide, benzyl chloride, benzene, and toluene) with nylon since these compounds do not have hydrogen-bonding capabilities. A suggested mechanism for their interactions with nylon cannot be given from the experimental data, even though it is attractive to conjecture that probably the interaction is primarily through dipole or Van der Waals' forces.

Water, the smallest molecule studied in the series, showed the greatest equilibrium sorption (4.4 mmoles/g.). The large number of moles of water sorbed is more than would be expected. Here it is assumed that a water molecule hydrogen bonds to the amide groups in the nylon. Since the activation energy of desorption is slightly less than the heat of vaporization (Table III), the additional water molecules sorbed by the nylon may be due to association of water molecules sorbed by the nylon matrix. Puffr and Sebenda (11), in fact, suggested from their studies that three molecules of water interact at two neighboring amide groups in nylon. As may be noted from Table II, acetic acid is also sorbed to a great extent by nylon (4.2 mmoles/g.). A comparison of the activation energy of desorption with the heat of vaporization of acetic acid (Table III) suggests that acetic acid may also be in an associated state within the nylon matrix and thus the interaction may be similar to the water-nylon interaction.

The aliphatic alcohols reveal that the size of the molecule plays an important role in the quantity of sorption occurring. As is clear from Table II, the equilibrium sorption decreases as the homologous series is ascended from methyl alcohol (2.6 mmoles/g.) to pentanol (0.16 mmole/g.). With these alcohols, the activation energies of desorption have values close to their heats of vaporization. This implies that the state of these molecules in nylon is similar to their liquid state. It is also interesting to observe from Table III that as the alcoholic series is ascended, the energy of activation increases from a value of 8.7 kcal./mole for methanol to 12.9 kcal./mole for pentanol. As was indicated previously, the activation energy of desorption may be considered as approximating the heat of sorption and, thus, as an indication of the strength of interaction. These results indicate the importance of the hydrophobic portion of the compounds in acting as secondary sources of interaction forces with the nylon, a suggestion consistent with hydrophobic bonding (12, 13). In the alcohol series, methanol has an activation energy of desorption similar to that of water.

Ethylene glycol, having a similar molecular size to propyl alcohol, was sorbed to the same extent as *n*-propyl alcohol (Table II). The activation energy of desorption (7.3 kcal./mole), however, is lower than the heat of vaporization (11.8 kcal./mole). It is possible that the molecule is interacting at an amide site through only one of its hydroxyl groups (one hydrogen bond rather than two hydrogen bonds which may occur in the liquid state). Introduction of a chloro-

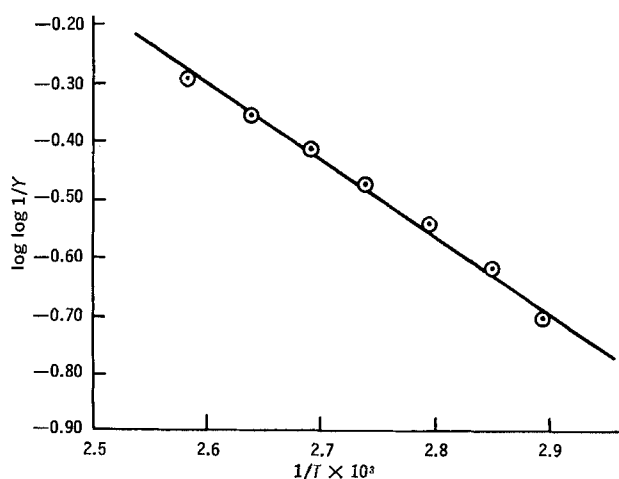


Figure 2—An example of a Broido (9) plot for benzyl alcohol.

ine atom to ethanol produces the compound 2-chloroethanol and increases the sorption from 2.1 mmoles/g. (for ethanol) to 3.3 mmoles/g. The activation energy of desorption for 2-chloroethanol was 5.1 kcal./mole, while its heat of vaporization was 11.8 kcal./mole. With the data available, it is difficult to postulate the reason or reasons for the high degree of sorption or to rationalize in a satisfactory manner the large difference between the activation energy of desorption and the heat of vaporization.

Chloroform is sorbed to a reasonable extent (1.53 mmoles/g.), similar to *n*-propanol (1.43 mmoles/g.). The bond strength of chloroform in nylon is approximately the same as the bond energy of chloroform in the liquid state.

Ethyl iodide was sorbed to a small extent by nylon, while ethyl bromide showed no significant sorption. Small sorption levels were also found for acetone and methyl acetate, but the rationale for these interactions cannot be presented in a satisfactory manner.

In general, the aromatic compounds, with the exception of phenol and benzyl alcohols, showed less tendency to be sorbed by nylon than the aliphatic compounds. Phenol interacted so strongly with nylon that it dissolved the polymer. Benzyl alcohol was sorbed to nearly the same extent as ethyl alcohol (Table II). The activation energy of desorption for benzyl alcohol was approximately one-half that of its heat of vaporization, indicating that the bond formation of the molecules in the liquid state is much stronger than exists when the molecules are in nylon. It may be assumed that both phenol and benzyl alcohol interact primarily through hydrogen-bond formation with nylon. Benzaldoxime is also sorbed but to a much lesser extent; since it also has an acidic hydrogen, the interaction may be through a hydrogen bond with nylon. Benzyl chloride, benzene, toluene, and acetophenone sorb to a small extent, but their mode of interaction is not clear.

Even though dipole moment values for the compounds are not referred to in this report, they were obtained for most of the compounds and were studied to see if any general relationship could be detected between the constant and sorption. No significant relationship was noted.

In reviewing the sorption behavior of the 39 compounds in this study, it is apparent that compounds having hydrogen-bonding capabilities (*i.e.*, OH or COOH groups) are most likely sorbed by nylon. Other structural features in the molecule can, however, increase or decrease the extent of sorption. Size of the molecule in a homologous or related series also plays an important role in the final equilibrium sorption process. Other compounds not having hydrogen-bonding capabilities may also be sorbed but generally to a much lesser extent than the hydrogen-bonding molecules.

SUMMARY

In the studies reported here, 39 compounds were investigated as to their interaction with nylon. Twenty of the compounds were significantly sorbed by the nylon. TGA permitted the determination of the equilibrium sorption weights of the compounds sorbed and the activation energies of desorption. A knowledge of these properties was helpful in drawing some general conclusions as to the mechanism of the interactions. TGA may be of practical value in

obtaining both kinetic and approximate thermodynamic data from sorption experiments when there is a need to evaluate or screen a large number of compounds as to their potential interaction with a polymeric material. Research in this field is continuing, and the results will be reported in subsequent publications.

REFERENCES

- (1) A. J. Kapadia, W. L. Guess, and J. Autian, *J. Pharm. Sci.*, **53**, 720(1964).
- (2) *Ibid.*, **53**, 28(1964).
- (3) M. B. Rodel, W. L. Guess, and J. Autian, *J. Pharm. Sci.*, **54**, 79(1965).
- (4) K. Stobaugh, J. Nematollahi, W. L. Guess, and J. Autian, *J. Dent. Res.*, **47**, 198(1968).
- (5) R. D. Schoenwald and P. F. Belcastro, *J. Pharm. Sci.*, **58**, 930(1969).
- (6) S. L. Madorsky, "Thermal Degradation of Organic Polymers," Interscience, New York, N. Y., 1964.
- (7) C. D. Doyle, in "Techniques and Methods of Polymer Evalua-

- tion I, Thermal Analysis," Marcel Dekker, New York, N. Y., 1966.
- (8) E. S. Freeman and B. Carroll, *J. Phys. Chem.*, **62**, 394(1958).
- (9) A. Broido, *J. Polymer Sci. A-2*, **7**, 1761(1969).
- (10) G. Oster, *J. Polymer Sci.*, **16**, 235(1955).
- (11) R. Puffr and J. Sebenda, *J. Polymer Sci., C*, **16**, 79(1966).
- (12) H. E. Schroeder and S. N. Boyd, in "Molecular Structure and Biological Specificity," L. Pauling and H. A. Itano, Eds., Waverly, Baltimore, Md., 1957, pp. 116-127.
- (13) H. Zollinger, *J. Soc. Dyers Colour.*, **81**, 345(1965).

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Action of Lysergide, Ephedrine, and Nimergoline on Brain Metabolizing Activity

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Abstract □ The effects of lysergide, ephedrine, and nimergoline on the metabolizing ability (demethylation and acetylation of aminopyrine and glucuroconjugation of oxazepam) of the dog brain isolated *in situ* were tested. The intracarotid perfusion with lysergide did not induce significant variations in aminopyrine and oxazepam metabolism, while the perfusion with ephedrine or nimergoline significantly increased the disappearance of the tested substances from the extracorporeal circuit, with an increase of some metabolic products. Activation of the tested biotransformation was accomplished by a decrease in cerebral vascular resistance and an increase in oxygen consumption. The action of lysergide, ephedrine, and nimergoline on the depression of the cerebral activity by hypoxia in dogs also was studied. Only ephedrine and nimergoline significantly improved the partial spontaneous reversion of the electroencephalogram depression, accomplished by a recovery of some enzymes (glutamic oxalacetic transaminase, lactate dehydrogenase, and alkaline phosphatase) in the cerebrospinal fluid, which was altered by the condition of hypoxia.

Keyphrases □ Metabolism, cerebral—lysergide, ephedrine, nimergoline effects, *in situ*, dogs □ Lysergide—cerebral metabolism effect, dogs □ Ephedrine—cerebral metabolism effect, dogs □ Nimergoline—cerebral metabolism effect, dogs

Many researchers have related changes in cerebral metabolism to changes in oxygen metabolism, cerebral blood flow, the electroencephalogram, and enzymes of the cerebrospinal fluid, for example. The present study was undertaken to investigate the action of lysergide, ephedrine, and nimergoline on these same parameters. To eliminate any interference from systemic response, the action of the drugs was investigated during a direct perfusion into the circle of Willis.

METHOD

The experiments were performed in the dog using two techniques: (a) the isolated perfused brain *in situ*, and (b) depression of cerebral activity by progressive hypoxia.

Isolated Perfused Brain *In Situ* Technique—Animals and Anesthesia—The experiments were carried out on 40 beagle dogs (10.7–14.6 kg. body weight), which were preanesthetized with urethan (0.4 g./kg. i.p.). Anesthesia was induced and maintained by nitrous oxide, cyclopropane, or ethyl ether in closed circuit. The animals were given artificial ventilation after tracheal intubation with a Warne tube, following succinylcholine chloride (1 mg./kg. i.v.) administration.

Operative Procedure—Benzi *et al.* (1) stated that the operative procedure consists mainly of the isolation of the external jugular veins and the common carotid arteries, with ligation of all their branches except the internal carotid arteries and the right thyroidea superior artery. In addition, the vertebral vessels are ligated before their entrance into the transverse foramen of C2 or C3. The numerous muscular branches arising from the vertebral vessels, the anastomosis between vertebral and carotid arteries, the anastomosis between vertebral and jugular veins, the internal jugular veins, the vascular branches of the neck, the vessels running under the carotid arteries and vagus nerves, and the zygomatic, maxillary, auricular, and supraorbital vessels are all occluded by ligation or compression. The occlusions of the sinus columnae vertebralis and the anterior spinal artery are made by opening the rachis in C2, ligating the spinal artery according to the method of Greeley and Greeley (2), and compressing the venous vessels around the spinal cord.

Both of the isolated jugular veins were ligated, cannulated, and connected to the venous reservoir of the pump-oxygenator system by gravitational flow. Both of the isolated carotid arteries also were cannulated and connected to the pump-oxygenator system. The isolated right thyroidea superior artery was cannulated by a polystan tube and connected to a perfusor apparatus (Palmer). Arterial blood pressure was measured from a cannula inserted into a femoral artery. Extradural electrodes were set in place some days before the experiments; during the experiments the electroencephalogram was