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# KINETICS AND THERMODYNAMICS OF DRUG PERMEATION THROUGH SILICONE ELASTOMERS IV. EFFECT OF POLYMER BACKBONE STRUCTURE

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## Abstract

The effect of silicone polymer backbone structure on the permeability of progesterone and testosterone through silicone membranes was investigated in the capsule-type drug delivery system at 25, 37 and 50°C, respectively. Three types of polymer were studied: (I) $(Me_2SiCH_2)_x$, (II) $(Me_2Si\text{-}C_6H_4\text{-}SiMe_2O)_x$, and (III) $[Me_2Si(CH_2)_nSiMe_2O]_x$, where n=2, 6 and 8.

Permeabilities of progesterone in these polymers were found to decrease in the following order: Polymer (III) > Polymer (I) > Polymer (II). The same order was also observed for the permeabilities of testosterone, but their values were one order of magnitude lower than those of progesterone. Incorporation of the phenylene group in the polymer backbone in Polymer (II) caused a significant decrease in the diffusion coefficient but an increase in the solubility coefficient. The net effect is a 50% decrease in the permeability with respect to $(Me_2SiO)_x$. This effect was found to be less pronounced with alkylene group in Polymer (III).





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The activation energies of permeation for progesterone through these polymers were found to be in the range of 12-21 kcal/mole.



## INTRODUCTION

Many publications have evolved from the evaluation of drug permeation through polydiorganosiloxane membranes[1-9]; however, very few, if any, papers have been published on the effects of polysiloxane backbone structure on the rate of drug release. Chemical and physical properties of silicone polymers are known to be dependent upon not only the substituents on silicone but also the polymer backbone structure. For example, if the organic substituents on silicone are held constant, e. g., Me, and the oxygen in the siloxane chain is replaced by other linkages, profound changes in glass transition temperature (Tg) and melting temperature (Tm) take place. This can be illustrated by replacing every other oxygen atom in the polydimethylsiloxane (PDMS) chain, $(Me_2SiO)_x$, with a $-CH_2CH_2-$ linkage, i. e., $(Me_2SiCH_2CH_2SiMe_2O)_x$ which results in a Tg increase from -123°C (PDMS) to -88°C. If every other oxygen atom is replaced with a $p\text{-}C_6H_4-$ linkage, even larger changes in the phase transition temperature take place[10]. The Tg and Tm become -18 and 148°C, respectively, as compared to -123 and -40°C respectively for PDMS .

The large changes in physical properties, resulting from the change in polymer backbone structure illustrated above, suggests that drug permeability of silicone polymers can be significantly changed by modifying the backbone structure of the polymer. The objective of this work was to systematically investigate the effect of polymer backbone structure on the

permeability of drug, using progesterone and testosterone as model drug compounds. The organic substituents on silicon were held constant, i. e., dimethyl groups, in order to eliminate the substituent effect. The following three types of polymer were investigated:

Polymer (I):

$(Me_2\ SiCH_2)_x$

Polymer (II):

$(Me_2Si\text{-}p\text{-}C_6H_4\text{-}SiMe_2O)_x$ and $(Me_2Si\text{-}m\text{-}C_6H_4\text{-}SiMe_2O)_x$

Polymer (III):

$[Me_2Si(CH_2)_nSiMe_2O]_x$, where n = 2, 6, and 8

Preliminary results are reported in this paper.

## EXPERIMENTAL

### (A) Materials

(1) Progesterone, testosterone (both purchased from Sigma Chemical Co.), and polyethylene glycol (PEG 400) (purchased from Fisher Scientific), were used as received.

(2) Silicone Polymers Preparation

(a) Polymer(I) - $(Me_2SiCH_2)_x$

To prepare the silmethylenesiloxane polymer, 1,1,3,3-tetramethyl -1,3- disilacyclobutane[11] was first synthesized followed by platinum catalysis[12] as shown below:

$$ClCH_2Me_2\ SiCl \xrightarrow{Mg/THF} Me_2Si\begin{array}{c}CH_2\\ \diagup\quad\diagdown\\ \diagdown\quad\diagup\\ CH_2\end{array}SiMe_2 \xrightarrow{Pt/C} (Me_2\ SiCH_2)_x$$

(b) Polymer (II) - $[Me_2Si\text{-}(C_6H_4)\text{-}SiMe_2O]_x$

To prepare the silphenylenesiloxane polymers, the required intermediates were synthesized by the "in-situ " Grignard reaction shown below:

$$HMe_2SiCl + ClC_6H_4Cl \xrightarrow{Mg/THF} HMe_2Si(C_6H_4)SiMe_2H$$

The intermediate was hydrolyzed to the diol and polymerized with a condensation catalyst to give polymer (II)[13]. Both poly(tetramethyl-p-silphenylene-siloxane) and poly(tetramethyl-m-silphenylene-siloxane) were prepared in this manner.

(c) Polymer (III) - $[Me_2Si(CH_2)_n\ SiMe_2O]_x$ where n = 2, 6, and 8. The intermediates for polymer (III) were prepared by the hydrosilation reaction shown below:

$$(ViMe_2Si)_2O + HMe_2SiCl \xrightarrow{Pt} (ClMe_2SiCH_2CH_2SiMe_2)_2O$$

$$CH_2{=}CH(CH_2)_xCH{=}CH_2 + HMe_2SiCl \xrightarrow{Pt} ClMe_2Si(CH_2)_{x+4}SiMe_2Cl$$

These chlorosilanes were hydrolyzed to give $HO-[Me_2Si(CH_2)_x\ SiMe_2O]_yH$, which was further condensed to give the desired polymers.

(3) Membrane Fabrication

The polymers thus prepared were crosslinked with an organic peroxide to give the desired membranes. It was found that if the membrane was flexible and too thin, it had a tendency to bow in the permeation cell thus changing its surface area during the experiment. The data thus generated were found to be erratic. To avoid this problem the thickness of the membrane was kept above 0.146 cm (with the exception of poly(tetramethyl-p-silphenylene-siloxane) which was very rigid at very thin thicknesses and was evaluated at 0.0128 cm.).

(B) Permeability, Diffusivity and Solubility Measurements

Permeability of progesterone and testosterone through the silicone membranes was investigated in the capsule-type

delivery system using the apparatus developed by Ghannam - Chien[14,15]. The experimental procedure for the permeability measurements was described in the companion paper[16]. The experiments were carried out in 40/60 v/v PEG 400/water solution at 25, 37 and 50°C, respectively. The intrinsic release rate, $(dQ/dt)_\infty$, was calculated from the apparent release rate, $(dQ/dt)_a$, using the following equation:

$$(dQ/dt)_\infty = (dQ/dt)_a/\gamma \qquad (1)$$

where $\gamma = 1 - 2d\,(dQ/dt)_a / Sh_R D_R C_s$ (2)

$D_R$ = diffusion coefficient of drug in the receptor phase ($9.81 \times 10^{-7}$ cm²/sec. for both progesterone and testosterone in 40/60 v/v PEG 400/water at 37°C).

$C_s$ = concentration of saturated drug solution in the donor phase (204µg/ml for progesterone and 432µg/ml for testosterone at 37°C in 40/60 v/v PEG 400/water).

d = length of the magnetic bar (2.54 cm)

$Sh_R$ = Sherwood number (379 at 425 r.p.m. stir rate in 40/60 v/v PEG 400 water at 37°C)

To correct for the difference in thickness from one membrane to another, the $(dQ/dt)_\infty$ thus obtained was multiplied by the membrane thickness, $\ell$.

Two methods were employed to determine the diffusivity coefficient of polymer, $D_p$, i.e., capsule-type release method and matrix-type release method as described previously[16]. In the former case, the following equation was used to calculate $D_p$.

$$D_p = \ell^2/6t_l \qquad (3)$$

where $\ell$ is the membrane thickness and $t_l$ is the time-lag. In the latter method $D_p$ was calculated from the following equation.

$$D_p = \left(\frac{Q/Q_\infty}{\sqrt{t}}\right)^2 \frac{\pi \ell^2}{16} \qquad (4)$$

where: $Q$ = Amount of drug permeated/unit area of membrane at time, t

$Q_\infty$ = Total amount of drug permeated/unit area of membrane

$\ell$ = Membrane thickness

Equation (4) can be applied only when $0<Q/Q_\infty<0.6$

The solubility coefficient, $C_p$, was calculated from the intrinsic rate of permeation and diffusion coefficient, $D_p$, as shown below:

$$C_p = (dQ/dt)_\infty \cdot \ell/D_p \qquad (5)$$

where $\ell$ is the membrane thickness.

## RESULTS AND DISCUSSION

### (A) Effect of Crystallinity

The drug permeability of $(Me_2Si\text{-}p\text{-}C_6H_4\text{-}SiMe_2O)_x$ was found to be extremely low. Negligible amount of progestrone permeated through the membrane even after seven days. $(Me_2Si\text{-}m\text{-}C_6H_4\text{-}SiMe_2O)_x$, on the other hand, gave reasonable permeability. Crystallinity was responsible for such a marked difference. The former was a highly crystalline material, whereas the latter was amorphous at room temperature. Thus only the latter was studied further in Polymer (II) series. Polymers (I) and (III) were all amorphous materials.

### (B) Effect of Polymer Backbone Structure

The intrinsic rate of permeation, $D_p$ and $C_p$ obtained with progesterone and testosterone at 37°C are summarized in Table 1. Data obtained with $(Me_2SiO)_x$ are also included for comparison purposes.

#### (1) Diffusion Coefficient, $D_p$

The $D_p$ of progesterone and testosterone in these polymers was about the same order of magnitude and both were

TABLE 1

INTRINSIC RATE OF PERMEATION, DIFFUSION COEFFICIENT, SOLUBILITY COEFFICIENT AND PARTITION COEFFICIENT AT 37°C

| Polymer | $(dQ/dt)^{\cdot}\ell$ $(\times 10^4)$ (mcg/cm-s) | $D_p (\times 10^7)$ ($cm^2/s$) | $C_p$ (mcg/$cm^3$) | K* |
|---|---|---|---|---|
| **(A) Progesterone** | | | | |
| $(Me_2SiCH_2)_x$ (I) | 2.98 | 1.08 | 2,760 | .074 |
| $(Me_2Si\text{-}m\text{-}C_6H_4SiMe_2O)_x$ (II) | 2.77 | 0.28 | 9,870 | .021 |
| $[Me_2Si(CH_2)_nSiMe_2O]_x$ (III) | | | | |
| n = 2 | 4.78 | 2.65 | 1,800 | .113 |
| n = 6 | 4.63 | 1.61 | 2,876 | .071 |
| n = 8 | 3.93 | 1.66 | 2,367 | .086 |
| $(Me_2SiO)_x$ | 5.67 | 9.03 | 628 | .325 |
| **(B) Testosterone** | | | | |
| $(Me_2SiCH_2)_x$ (I) | 0.243 | .66 | 368 | 1.17 |
| $(Me_2Si\text{-}m\text{-}C_6H_4SiMe_2O)_x$ (II) | 0.681 | .26 | 2,560 | .17 |
| $[Me_2Si(CH_2)_nSiMe_2O]_x$ (III) | | | | |
| n = 2 | 0.457 | 2.56 | 179 | 2.41 |
| n = 6 | 0.531 | 1.54 | 344 | 1.26 |
| n = 8 | 0.538 | 1.34 | 411 | 1.05 |
| $(Me_2SiO)_x$ | 0.555 | 6.55 | 85 | 5.08 |

*$K = Cs/C_p$, Cs = 204 mcg /$cm^3$ for progesterone and 432 mcg /$cm^2$ for testosterone

found to decrease in the following order:

$(Me_2SiO)_x$ > $[Me_2Si(CH_2)_nSiMe_2O]_x$, (III) > $(Me_2SiCH_2)_x$, (I) > $(Me_2Si\text{-}m\text{-}C_6H_4\text{-}SiMe_2O)_x$, (II)

Replacement of every other oxygen atom in $(Me_2SiO)_x$ with a m- phenylene linkage [Polymer (II)] caused a decrease in $D_p$ by at least one order of magnitude. When every other oxygen atom was replaced with an alkylene linkage, the effect was not as pronounced as the phenylene linkage. The introduction of phenylene linkage to the siloxane backbone apparently induced more rigidity to the siloxane chain than the alkylene linkage. When all oxygen atoms in $(Me_2SiO)_x$ were replaced with a methylene linkage [Polymer (I)], the polymer chain became as rigid as Polymer (II), resulting in a very low $D_p$ value. The $D_p$ of $(Me_2SiCH_2)_x$ was almost one order of magnitude lower than that of $(Me_2SiO)_x$.

In the companion paper, an attempt was made to interpret the $D_p$ in terms of the free volume model[16]. A good correlation was obtained between $D_p$ and compressibility of $(MeRSiO)_x$. To verify whether or not the same correlation held in the three classes of polymer studied in this work, $D_p$ values were plotted against the compressibility. Data obtained with $(MeRSiO)_x$ were also included for comparison purposes. Results are shown in Figures 1 and 2 for progesterone and testosterone. The linear correlation coefficients for progesterone and testosterone were found to be 0.94 and 0.96 respectively. Thus there appears to be a good correlation between $D_p$ and compressibility of the silicone polymers investigated so far. More work on the interpretation of $D_p$ based on the free volume model[17,20] and the molecular model[21] are planned.

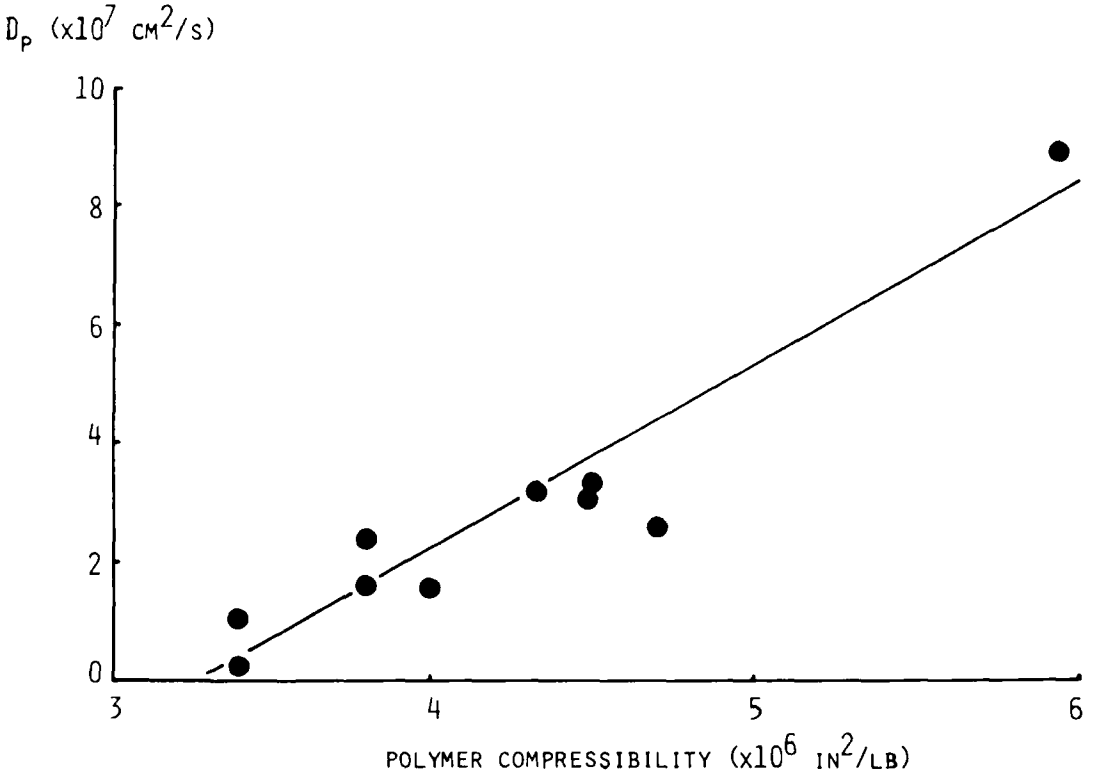


FIGURE 1

Diffusion coefficient ($D_p$) of Progesterone at 37°C vs. polymer compressibility.

(2) Solubility Coefficient, $C_p$

The solubility coefficients, $C_p$, of both progesterone and testosterone were found to increase in the following order:

$$(Me_2SiO)_x < [Me_2Si(CH_2)_nSiMe_2O]_x, \text{ (III)} \sim (Me_2SiCH_2)_x, \text{ (I)} \ll [Me_2Si\text{-}m\text{-}C_6H_4\text{-}SiMe_2O)_x, \text{ (II)}$$

The absolute values of $C_p$ for testosterone, however, were lower than those of progesterone. This was the major

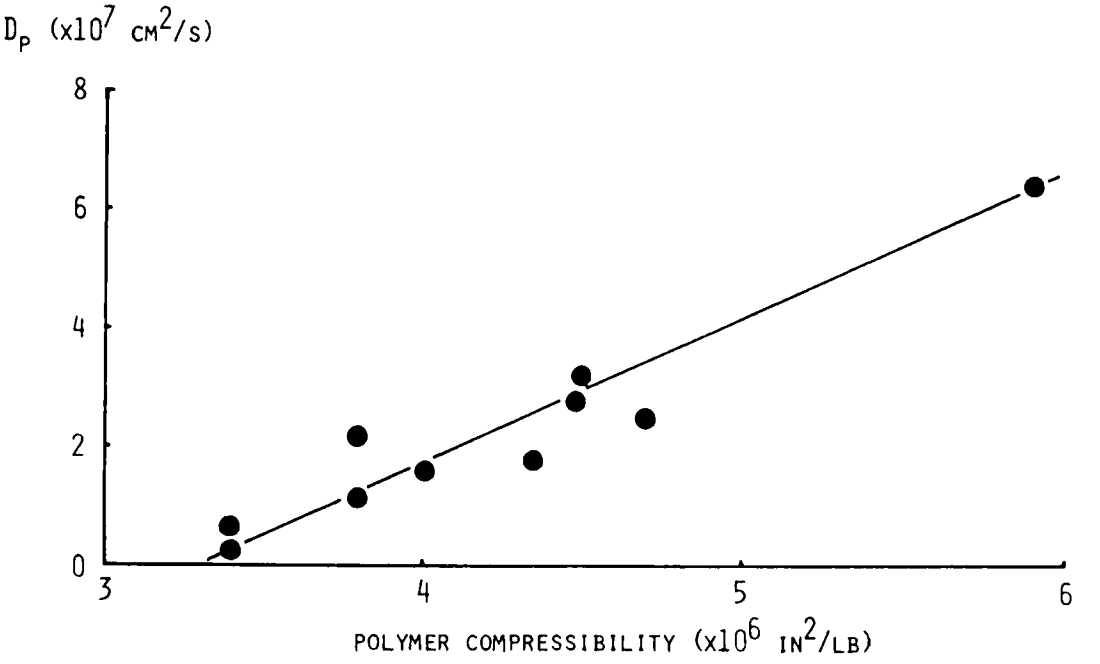


FIGURE 2

Diffusion coefficient ($D_p$) of testosterone at 37°C vs. polymer compressibility

contributing factor to the reduced permeability of testosterone when compared to progesterone (by an order of magnitude) in the polymers we investigated.

In the $(MeC_nH_{2n+1}SiO)_x$ series, it was shown that the $C_p$ of both progesterone and testosterone increased linearly with the number of carbons in the pendent alkyl group[16]. A question arose as to whether or not the same relation held in polymer (III), in which an alkylene linkage was incorporated into the polymer backbone. Figure 3 shows a plot of $C_p$ vs. the number of carbons in the alkylene linkage. Experimental data obtained with $(MeC_nH_{2n+1}SiO)_x$ were included for comparison purposes. Although the data showed some scatter in

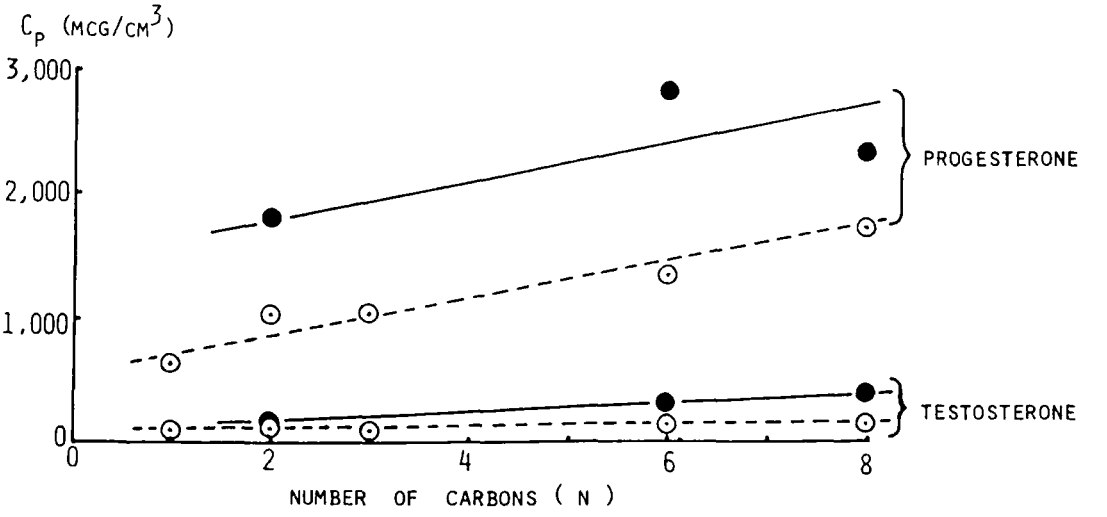


FIGURE 3

Effect of number of carbons in alkyl/alkylene group on $C_p$
——●—— backbone alkylene group: $[Me_2Si(CH_2)_nSiMe_2O]_x$
---⊙--- pendent alkyl group: $(MeC_nH_{2n+1}SiO)_x$

the progesterone series, the results confirmed that $C_p$ did increase linearly with the number of carbons in both backbone alkylene group, as well as pendent alkyl group. Thus $C_p$ was expressed empirically by:

$$C_{p,n} = C_{p,o} + AN$$

where $C_{p,n}$ was the solubility coefficient in the nth congener of the polymer, $C_{p,o}$ was the solubility coefficient in the hypothetical zero chain length and A was a constant whose magnitude was dependent upon the penetrant. Figure 3 shows that the value of $C_{p,o}$ associated with backbone alkylene linkage is higher than that associated with the pendent alkyl group.

(3) Permeability

The intrinsic rate of permeation, $(dQ/dt)_\infty \cdot \ell$, for the progesterone series decreases in the following order:

$(Me_2SiO)_x$ > $[Me_2Si(CH_2)_nSiMe_2O]$, (III) > $(Me_2SiCH_2)_x$, (I) > $(Me_2Si\text{-}m\text{-}C_6H_4\text{-}SiMe_2O)_x$, (II)

The difference between the permeability of $(Me_2SiO)_x$ and that of Polymer (II) is only about 50%, which is much less than the differences observed with $D_p$ and $C_p$. This is caused by the fact that the permeability is the product of $D_p$ and $C_p$, and the modification of polymer backbone structures affects $D_p$ and $C_p$ in opposite ways. That is, the replacement of every other oxygen atom with a phenylene linkage causes a marked decrease in $D_p$, but a significant increase in $C_p$ by about the same order of magnitude. The gain in $C_p$ compensates for the decrease in $D_p$, resulting in a marginal change in the intrinsic release rate in Polymer (II). This was also found to be the case in the Polymer (I) and (III) series.

The permeabilities of testosterone through these polymers were found to be about one order of magnitude lower than those of progesterone. This was primarily caused by the lower solubility coefficients of testosterone when compared to those of progesterone, as shown in the $(Me(C_nH_{2n+1}SiO)_x$ case reported elsewhere[16].

The effect of backbone structure on the permeability of testosterone followed the same pattern as that of progesterone.

(C) Effect of Temperature

The activation energy, $\Delta E$, of permeation for progesterone through these three classes of polymer are shown below:

| | Polymer | $\Delta E$ ( Kcal / mol ) |
|---|---|---|
| (I) | $(Me_2SiCH_2)_x$ | 11.8 |
| (II) | $(Me_2Si\text{-}m\text{-}C_6H_4\ SiMe_2O)_x$ | 14.5 |

| (III) $[Me_2Si(CH_2)_nSiMe_2O]_x$ | |
|---|---|
| n = 2 | 14.6 |
| n = 6 | 17.7 |
| n = 8 | 21.5 |

Incorporation of an alkylene group into the polymer backbone [i.e., Polymer (III)] resulted in much higher ΔEs than those obtained with the pendent alkyl group [i.e., $(MeC_nH_{2n+1}SiO)_x$] reported earlier[16]. These are compared below:

| | ΔE ( kcal /mole) | | |
|---|---|---|---|
| | n = 2 | n = 6 | n = 8 |
| $[Me_2Si(CH_2)_nSiMe_2O]_x$ | 14.6 | 17.7 | 21.5 |
| $[MeC_nH_{2n+1}SiO]_x$ | 12.5 | 15.6 | 15.8 |

Interpretation of these data in terms of mathematical models will be attempted in the future.

## CONCLUSIONS

The effect of silicone polymer backbone structure on the permeability of progesterone and testosterone through the following three types of silicone membranes was investigated: (I) $(Me_2SiCH_2)_x$, (II) $(Me_2Si\text{-}C_6H_4\text{-}SiMe_2O)_x$, and (III) $[Me_2Si(CH_2)_nSiMe_2O]_x$, where n = 2, 6 and 8.

Permeabilities of progesterone through these polymers were found to decrease in the following order: Polymer (III) > Polymer (I) > Polymer (II). The same order was also observed for the permeabilities of testosterone, but their values were one order of magnitude lower than those of progesterone .

Incorporation of the phenylene group in the polymer backbone [Polymer (II)] caused a significant decrease in the

diffusion coefficient but an increase in the solubility coefficient. The net effect was a 50% decrease in the permeability with respect to $(Me_2SiO)_x$. Such an effect was found to be less pronounced with alkylene groups in Polymer (III).

A good linear correlation between $D_p$ and compressibility of Polymers (I), (II), (III) and $(MeRSiO)_x$ was established. This suggests that the free volume model might be applicable in interpreting the effect of polymer structure on $D_p$.

The activation energies of permeation for progesterone through these polymers were found to be in the range of 12-21 kcal /mole.

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