DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 16(14), 2077-2095 (1990)

LIQUID-CRYSTALLINE SIDE-CHAIN SILASTOMERS, LARGLY MODIFIABLE DIFFUSION MEDIA FOR THE CONTROL OF DRUG DELIVERY.

H. Loth* and A. Euschen
Institute for Pharmaceutical Technology,
Universität des Saarlandes,
D-6600 Saarbrücken,
Federal Republic of Germany

Dedicated in friendship to Prof. Dr. K.H. Frömming, Berlin, on the occasion of his 65. birthday

ABSTRACT

Liquid-crystalline side-chain polysiloxane elastomers were synthesized in such a manner as to give thin foils that can be used as diffusion-controlling membranes or drug-loaded matrices. The structure and the properties of the silastomers can be modified by the type of polysiloxane main chain, the chain length of the dimethylpolysiloxane crosslinker and by the mesogenic group. The mesogens under investigation are 4-methoxyphenyl-4'-alkenyloxybenzoates with different

* to whom correspondence should be addressed

lengths of the spacer. The type and the content of the mesogenic group strongly influence the permeability of the membrane. If polymers with the same type of mesogen are compared, the logarithms of the diffusion coefficients of the model drug, salicylic acid, in the LC-silastomers are linearly correlated to the mole fractions of mesogen, indicating low permeabilities at high mesogen contents. Further, the permeability depends on the state of the phases of the mesogenic domains: The diffusivity is much smaller and the activation energy much higher in the LC state at lower temperatures than in the isotropic state of the silastomer at higher temperatures; there is a distinct change in the region of phase transition. The saturation concentration of salicylic acid in the polymers increases with increasing mesogen content. Again, the type of the mesogenic group exerts an influence. Further, the solubility of the drug is higher in the LC state of the silastomer at lower temperatures than in the isotropic state. All these properties together offer multifarious possibilities to adjust the drug release to the pharmacodynamic and pharmacokinetic requirements. The importance of the state of order to the permeability of a diffusion medium and the comparability with other liquid-crystalline systems, such as biological membranes, are discussed.

INTRODUCTION

Control of substance transport by diffusion is a widespread phenomenon in biology and technology. Because the diffusivity is dependent on the viscosity, the rate of diffusive transport is strongly influenced by the state of the diffusion medium, such as liquid

or liquid-crystalline. Therefore, transition from one phase to the other is accompanied by a considerable change in diffusion resistance. Advantage is derived from this principle by biological systems such as membranes, but less by technological ones. In previous reports, we introduced LC side-chain silastomers as drug delivery controlling media[1,2].

Liquid-crystalline side-chain polysiloxane elastomers ("LC silastomer") were first synthesized by Finkelmann et al.[3]; a generalized partial structure is seen in Fig. 1. Modifications of the chain lengths indicated in the formula by letters give a group of LC polymers showing phase transitions from the liquid-crystalline (LC) to the isotropic (I) state in the range from about 5 to 95°C, that is suitable for medical and pharmaceutical applications.

MATERIALS AND METHODS

Synthesis of LC Silastomers

1.5 g of a mixture of the reactants (Tab. 1), dissolved in 4.5 g toluene, is polymerized in the presence of 50 ppm platinum catalyst (dicyclopentadienylplatiniumchloride [4,5]) under nitrogen atmosphere at 60°C according to Finkelmann et al.[3]. The reaction mixture is composed of poly(methylsiloxane) (number of methylsiloxane units of the main chain $n = x + y = 60$; Wacker-Chemie GmbH, D-München 22) as the main chain, α,ω-divinyl-poly(dimethylsiloxane) ($v = 10$ or 25; Wacker-Chemie GmbH, D-München 22) as the crosslinker, the mesogens and the catalyst (the symbols refer to Fig. 1). Modified LC-silastomers are provided by suitably varying the part of the cross-

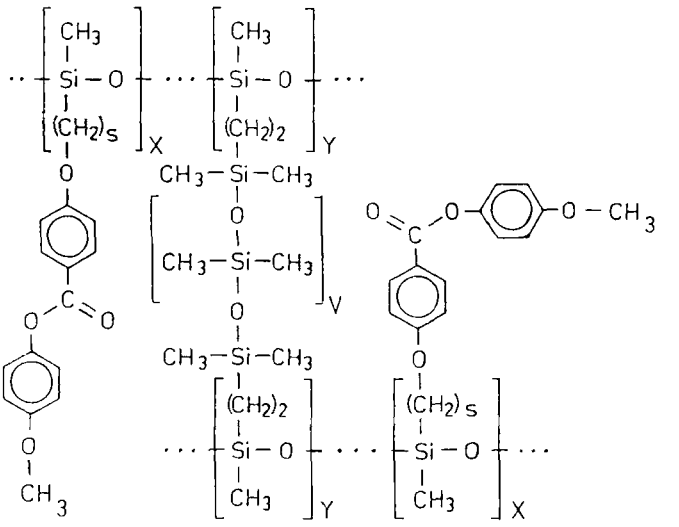

FIGURE 1

General structure of the LC-silastomers;
x = number of mesogenic groups at a main chain,
y = number of crosslinks at a main chain,
v = number of dimethylsiloxane units of the cross-linker,
s = number of methylene units of the spacer.

linker and of the mesogens, which are 4-methoxyphenyl-4'-alkenyloxybenzoates with spacer lengths of 3, 4 or 6 C-atoms (synthesized by known literature methods).

To obtain thin foils of constant thickness(about 300 µm) and without any holes and cracks, the reaction solution is filled into a cylindrical polytetrafluoroethylene (PTFE) vessel (diameter: 11 cm) with a plainly ground and polished bottom. The beaker is put into a tightly closing aluminium chamber, supplied with 2 valves enabling the air to be displaced by nitrogen; this apparatus is horizontally adjusted.

TABLE 1

Mixtures of the Reactants to obtain modified Types of LC Silastomers

LC silastomer type	main chain (mg/g)	crosslinker (mg/g)	mesogen	
			(mg/g)	mole fraction
45/15.25/3	118.3	480.2	401.5	.145
48/12.25/3	127.1	412.8	460.1	.176
51/9 .25/3	137.3	334.5	528.2	.218
54/6 .25/3	149.3	242.5	608.2	.274
54/6 .25/4	145.0	235.4	619.6	.274
54/6 .25/6	137.0	222.4	640.6	.274
45/15.10/3	160.3	295.9	543.9	.228
51/9 .10/3	168.0	186.0	646.0	.305
54/6 .10/3	172.1	127.1	700.8	.355

After 18 hours, the substances that have not reacted are withdrawn from the swollen polymer by toluene; then the latter is very slowly removed by methanol to transform the gel into a foil. This procedure needs about 3 days. Finally, the foil is freed from residual solvents by evaporation at 80°C and 0.1 mbar. Yield: 85-90%.

For the purpose of comparison, foils are produced from the nonliquid-crystalline SilGel 600 (Wacker-Chemie GmbH, D-München 22).

Permeability Measurements

A synthesized membrane (diffusion area: 9.62 cm^2) is mounted in a two-compartment diffusion cell similar to that described by Holmes et al. [6] (donor: a buffered 0.018 molar aqueous salicylic acid solution, pH 2.9 at room temperature; acceptor: buffer pH 7.4; temperature range between 20°C and 80°C with intervals of 5°C). The drug concentration in the acceptor is photometrically measured (continuously by means of a circulating system and a flow-through cell); data are recorded on line.

The pH-value of the donor is measured at each temperature at which the diffusion measurement is performed; it is standardized by comparison to buffers with known temperature dependence (DIN). The temperature dependence of the pK_a-values of salicylic acid is estimated by titration of sodium salicylate with hydrochloric acid according to Binder and Ebel [7] as well as Frosch [8]. The pH- and pK_a-values are used to calculate the membrane-permeable, undissociated part of the salicylic acid (required for the kinetic evaluations) at each experimental temperature.

Preliminary experiments showed that unstirred layers adjacent to the membrane may be ignored. Therefore, the permeability measurements can be evaluated by quasi-steady state monolayer diffusion kinetics derived from Fick's first law assuming a perfect sink acceptor.

Matrix Release Measurements:

To load the LC silastomers with drug, the foils are shaken in a solution of salicylic acid in a methanol-toluene mixture (8+2) until the equilibrium is reached a few days later. After evaporation of the solvent, particles of salicylic acid adhering to the foil surface are removed by methanol.

The loaded foil is attached to the above mentioned diffusion cell, one compartment of which is filled with the acceptor solution. On the other side of the membrane, a PTFE-plate gives support against the hydrostatic pressure. The salicylic acid release is measured as described above. The released amount of drug plus the amount left in the matrix and estimated by extraction with ethyl acetate yields the loaded quantity.

Other Methods:

The thickness of the synthesized foils is measured with an accuracy of ± 1 µm by a thickness meter model 5041 type VRZ 181 with a caliper MT 10 B (Heidenhain, D-Traunreut).

Thermal studies are performed by the Thermal Analyzer 990 with the DSC Cell 910 (Du Pont Instruments) and with a polarization microscope with heating stage Ortholux II Pol-BK (Ernst Leitz GmbH, D-Wetzlar).

RESULTS AND DISCUSSION

The synthesized membranes consist of LC-silastomers which are differentiated by the number, y, of crosslinks at a main chain, the number, x, of mesogenic groups at a main chain (x + y = 60 reflects the length of the main chain), the number, v, of dimethylsiloxane units of the crosslinker and the number, s, of methylene units of the spacer that connects the mesogen with the main chain. These indices are used to characterize the investigated polymers by the following code: x/y.v/s.

The siloxane network structure and the mesogenic side chains are affected by the executed modifications: Changing the proportions of the crosslinker and the mesogen as indicated in Tab. 1 results in crosslinking at each 4. to 10. methylsiloxane unit of the main chain and in mesogen contents between about 40 and 70% by weight. With the exception of the type 54/6.25/6, that is smectic, all other silastomers mentioned in Tab. 1 show nematic phases in the LC state.

Further modifications are easily realized by the use of different types of main chains (for instance a copolymer of methyl- and dimethylsiloxane units) and of mesogens which can manifoldly be varied [2,3].

The permeation of salicylic acid as ionogenic drug model through the LC-silastomer membranes gives linear first-order plots in semilogarithmic concentration-time diagrams $[\ln(c_o/c)/t]$ in the temperature range from 20°C to 80°C [1] (c = concentration in the donor, index o for t = 0). From the slopes of these lines the permeability coefficients, $P = D \cdot k_D$, and diffusion coefficients, D, can be calculated (Tab. 2).

TABLE 2

Diffusion Coefficients of Salicylic Acid in LC-Silastomers at various Temperatures in Comparison to a non-liquid-crystalline Silastomer and LC-I Phase Transition Temperatures evaluated by Arrhenius Plot Interpolation and by DSC Measurements

LC-silastomer code x/y.v/s	mesogen mole fraction X_m	diffusion coefficient $D \cdot 10^8 (cm^2 \cdot s^{-1})$ at the temperature							phase transition temperature (°C)	
		20°C	30°C	40°C	50°C	60°C	70°C	80°C	Arrhenius plot	DSC
SilGel 600	0	42.4	60.0	80.9	108	137	170	217	--	--
45/15.25/3	.145	.968	1.99	4.25	8.88	19.5	28.8	43.9	62	43
48/12.25/3	.176	.456	1.04	2.44	5.44	12.7	20.6	32.3	65	47
51/9 .25/3	.218	.155	.506	1.50	3.76	9.71	17.1	26.9	59	51
54/6 .25/3	.274	.020	.119	.644	1.82	5.73	11.0	19.8	53	63
54/6 .25/4	.274	.039	.155	.556	1.57	3.58	7.42	19.3	--	69
54/6 .25/6	.274	.121	.379	1.29	3.28	7.49	15.7	28.0	--	91
45/15.10/3	.228	.067	.324	1.12	2.94	7.55	14.2	22.9	57	38
51/9 .10/3	.305	.018	.088	.406	1.39	4.97	9.41	18.1	55	55
54/6 .10/3	.355	.006	.036	.191	.770	2.73	6.18	12.9	56	55

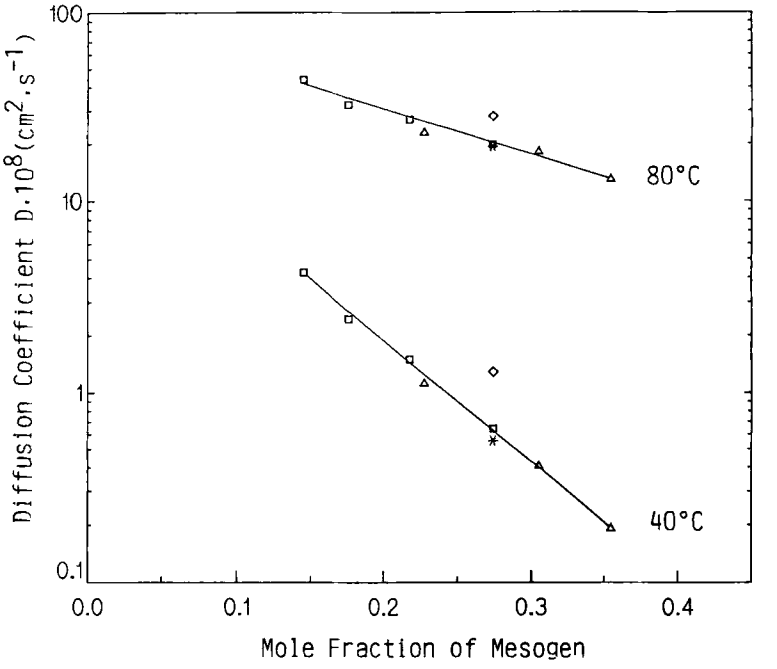

FIGURE 2

Semilogarithmic diagram of the diffusion coefficients of salicylic acid as a function of the mesogen contents of the LC polymers at 40 and 80°C. The values of the silastomer types (v/s) 10/3 and 25/3 only are included in the regression calculation. Polymer type (v/s): 10/3 △ , 25/3 □, 25/4 * , 25/6 ◇.

The predominant influence of the content and type of the mesogenic groups on the permeability of the silastomers is clearly seen in Fig. 2. Independent of the chain lengths of the crosslinkers, straight regression lines were obtained from the logarithms of the diffusion coefficients and the mole fractions of the mesogen when only the compounds with the C_3-spacer are considered. The higher the mesogen content, the tighter the silastomer becomes as a diffusion medium,

both in the liquid-crystalline and in the isotropic state. A prerequisite for the linear relationship between log D and the mesogen mole fraction is that all the LC silastomers are in the same state of phase, i.e. liquid-crystalline or isotropic, as is realized by the examples in Fig. 2 at 40 and 80°C. This is a question of the experimental temperature, and there may be the one or the other divergence because of the differing phase transition temperatures depending on the mesogen contents.

Changing the type of the mesogenic group can alter the permeability and the phase transition temperatures to a greater or lesser extent. The elongation of the spacer from 3 to 4 C-atoms increases the LC-I transition from 63° to 69°C, but the diffusion coefficients hardly differ in the two elastomer types, if they are compared at temperatures with the same state of phases (Tab. 2 and Fig. 2). On the other hand, a spacer with 6 C-atoms gives a LC silastomer with a considerably higher phase transition temperature (91°C) showing greater diffusion coefficients between 20° and 80°C, although it is in the LC state within the whole temperature range, whereas the polymer with the C_3-spacer is isotropic above 60°C approximately. This surprising fact can be explained by different arrangements of the mesogenic groups in the LC domains within the polymer network, depending on the length of the spacer as described by Schwarz [9]

By comparing the diffusion coefficients of one polymer type at different temperatures with each other, it may be recognized that the diffusion coefficients rise more strongly above the LC-I phase transition temperature (Tab. 2). That indicates that the

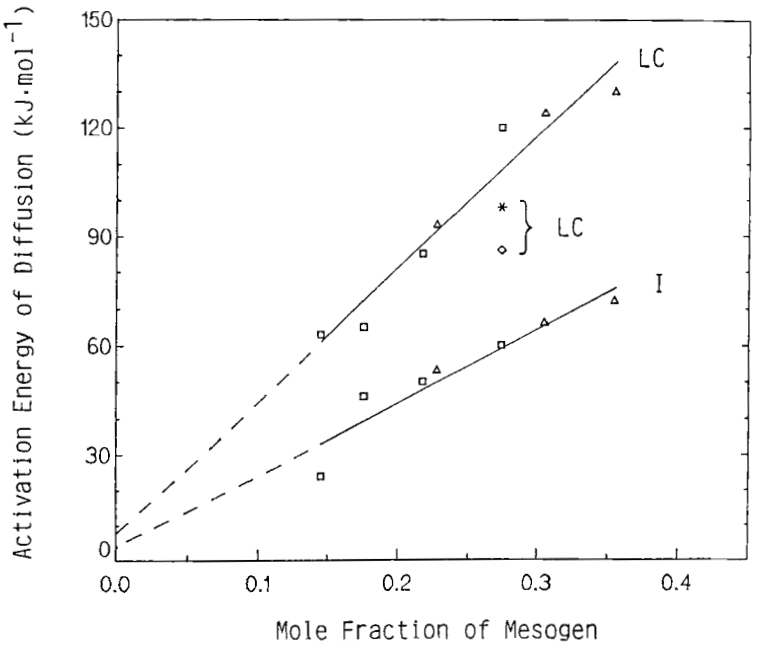

FIGURE 3

Activation energies of the diffusion of salicylic acid in LC silastomer media in the liquid-crystalline and isotropic state as functions of the mole fractions of the mesogen. The values of the silastomer types (v/s) 10/3 and 25/3 only are included in the regression calculation. Polymer type (v/s): 10/3 △, 25/3 □, 25/4 * , 25/6 ◇.

permeability of a membrane sharply increases within a fairly small temperature range exceeding the LC-I transition region. The Arrhenius plots for the log D (or log P) values versus the reciprocal degrees Kelvin show lines that change their slopes at specific temperatures corresponding to the LC-I phase transitions [1]. The steeper slope at lower temperatures belongs to the LC region which has a comparatively low permeability causing a high activation energy of

diffusion. In contrast, the membranes that have changed into the isotropic state are much more permeable. Accordingly, the activation energy of diffusion is smaller, corresponding to a lower slope in the Arrhenius diagram. It follows from these facts that the temperature-dependent control of diffusive transport operates more sensitively in the LC than in the isotropic state. Beside a general importance, this can be imagined as having regulating functions in biological systems, for instance in the horny layer of the skin.

The considerable differences between the activation energies of diffusion in the liquid-crystalline and in the isotropic state are seen in Fig. 3. Further, the activation energies are linearly correlated to the mole fractions of mesogen in both states, if membranes with the same mesogenic group but with different chain lengths of the crosslinker are included in the regression. On the other hand, changing the mesogenic group results in deviations, and it is already sufficient to modify the spacer or the alkoxy group at the end of the mesogen [2].

These results illustrate the principles how to design membranes with definite permeabilities adjusted to pharmacodynamic and pharmacokinetic necessities. Only a few modified polymers are mentioned in this article; they are materials with diffusivities differing by factors of 55 at 30°C and 22 at 40°C. In addition, there is an extensive chance to vary the polymer structures connected with a change in their permeabilities and in the temperature dependence of their properties.

LC-silastomers may not be taken as diffusion controlling membranes only, they can also be useful as drug-charged matrices for controlled delivery. The liberation of salicylic acid from such a matrix follows m/√t-linearity according to Higuchi's equation [10]:

$$m = \sqrt{(2A_o - c_s) \cdot c_s \cdot D \cdot t} \qquad \text{(Equ. 1)}$$

m = mass, A_o = drug concentration, c_s = saturation concentration, t = time.

The slopes of the m/√t-lines decrease with increasing mesogen content of the polymer matrix, which is analogous to the diffusivity of salicylic acid in the LC silastomers (Tab. 3), but obviously the ratios of the m/√t-values are much smaller than those of the diffusion coefficients comparing two definite polymer types with differing mesogen contents.

To understand these results the solubility of the drug in the LC silastomer materials must be regarded as an important factor. First, the saturation concentration of salicylic acid in a crosslinked polysiloxane without mesogenic groups (SilGel 600) is considerably lower (0.21% at 20°C) than in the LC polymers. The mesogenic domains act as a solvent, so that the solubility linearly increases with the mesogen content at a constant temperature, if the type of mesogen is the same in all polymers (Tab. 4). This is evident as seen in the column $(c_{s,p} - c_{s,o})/X_m$. However, mesogenic groups with an extended spacer (C_4 or C_6) show a markedly altered dissolution power for the salicylic acid. The relatively small ratios of the above mentioned m/√t-values can now be explained: The diffusion

TABLE 3

Release of Salicylic Acid (A_o = 0.5 mmol·cm^{-3}) from LC Silastomer Foils at 20° and 40°C and the corresponding Diffusion Coefficients estimated by Permeation Measurements

LC-silastomer code x/y.v/s	mesogen mole fraction X_m	matrix release $(m/\sqrt{t})\cdot 10^8$ (mol·cm^{-2}·s$^{-1/2}$)	diffusion coefficient $D\cdot 10^8$ (cm^2·s^{-1})
		temperature: 20°C	
45/15.25/3	0.145	3.30	0.968
54/6 .25/3	0.274	1.58	0.020
54/6 .10/3	0.355	1.35	0.006
		temperature: 40°C	
45/15.25/3	0.145	5.74	4.25
54/6 .25/3	0.274	2.84	0.644
54/6 .10/3	0.355	1.55	0.191

coefficients become smaller, but the saturation concentrations increase with growing mesogen content. Because of these opposed tendencies, the product $D\cdot c_s$, and therefore $m/\sqrt{t}$ too, show a lesser change than D by itself.

As a matter of course, the drug distribution which is relevant to the membrane permeability alters with the solubility; hence, it follows that the partition coefficients, c_p/c_w, linearly increase with

TABLE 4

Saturation Concentrations of Salicylic Acid in LC Silastomers in Dependence on the Mesogen Content at 20°C and Partition Coefficients in the System LC Silastomer/Water at 40 and 80°C ($c_{s,o}$ = Solubility in the non-liquid-crystalline SilGel 600).

LC silastomer code x/y.v/s	mesogen mole fraction X_m	saturation concentration $c_{s,p}$ (%)	$\frac{c_{s,p} - c_{s,o}}{X_m}$ (%)	partition coefficients $k_D = c_p/c_w$ at 40°C	at 80°C
SilGel 600	0	.21	---	.56	.42
45/15.25/3	.145	2.23	13.9	4.6	1.9
48/12.25/3	.176	2.70	14.1	5.6	2.2
51/9 .25/3	.218	3.16	13.5	6.2	2.4
45/15.10/3	.228	3.32	13.6	6.5	2.5
54/6 .25/3	.274	3.81	13.1	7.3	2.8
51/9 .10/3	.305	4.25	13.2	7.8	2.8
54/6 .10/3	.355	4.81	13.0	8.6	3.0
54/6 .25/4	.274	2.91	9.9	6.8	3.5
54/6 .25/6	.274	1.77	5.7	4.3	2.5

the mesogen level, as well (Tab. 4) (c_p = concentration in the polymer, c_w = concentration in the water phase). The temperature dependence of the distribution coefficients results from the decreasing solubility of salicylic acid in the LC-silastomers with rising temperature and from the opposed tendency of the solubility in water. Furthermore, the solubility depends on the state of the mesogenic domains: On passing the phase transition temperature, there is a leap in the temperature dependence of both the solubility and the partition coefficient. But, in the liquid-crystalline and in the isotropic state, both the solubility and the partition coefficient decrease with rising temperature and increase with the mesogen content; these dependences show steeper slopes in the liquid-crystalline than in the isotropic state.

As these studies show, LC silastomers offer many possibilities to modify membrane or matrix controlled release, so that the drug delivery can be adjusted to pharmacodynamic and pharmacokinetic conditions. Binding mesogenic groups with different chemical structures to the polysiloxane chains broadens the scope of variants. It may not be surprising that the diffusivity in the LC silastomers depends on the content of mesogenic groups filling in the meshes of the polymer network [9], but it has to be noted that relatively small changes of mesogenic structures, such as the lengthening of the spacer, can considerably alter the properties of the silastomers. Looking for the reasons, the molecular arrangement of the polymer has to be taken into consideration. The force of the interactions between neighbouring groups depends on the chemical structure of the mesogen, but

the degree of order in the LC domains can be limited by the length and mobility of the spacer groups. The main chains and the crosslinkers are probably involved, too. Hence, the diffusivity and the dissolving power are connected with structural parameters in a complex manner suggesting further theoretical considerations.

Possibly, LC side chain silastomers can be suitable models for other liquid-crystalline systems, such as biological membranes or the lipid layers of the stratum corneum, for instance. What is the importance of the state of order of the horny layer lipids to the permeability and the solubility of the xenobiotics in these lipids? These investigations of the LC side-chain silastomers have shown that the diffusivity in a LC medium is much smaller than in an isotropic medium. As we can understand, the free volume for the diffusive jumps decreases with increasing degree of order. Further, the degree of order influences the dissolving power, but a change in solubility indicates a change of the activity of a solute, too. Analogies to the ordered multiple lipid layers in the stratum corneum [11] seem to be obvious. Possibly, we can get a better insight into the mechanisms of skin permeation, of penetration enhancement and of the occlusion effect, by studying suitable model systems [12].

ACKNOWLEDGMENTS

This work is supported by the Deutsche Forschungsgemeinschaft, Fonds der Chemischen Industrie and Wacker-Chemie GmbH to which we express our thanks.

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