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Photodimerization and photopolymerization of amphiphilic cinnamic acid derivatives in oriented monolayers, vesicles and solution

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SUMMARY:

Cinnamic acid moieties were incorporated into amphiphilic compounds containing one and two alkyl chains. These lipid-like compounds with photoreactive units undergo self-organization to form monolayers at the gas-water interface and bilayer structures (vesicles) in aqueous solutions. The photoreaction of the cinnamic acid moiety induced by 254 nm UV light was investigated in the crystalline state, in monolayers, in vesicles and in solution in organic solvents. The single-chain amphiphiles undergo dimerization to yield photoproducts with twice the molecular weight of the corresponding monomers in organized systems. The photoreaction of amphiphiles containing two cinnamic acid groups occurs via two mechanisms: The intramolecular dimerization produces bicycles, with retention of the molecular weight of the corresponding monomer. The intermolecular reaction leads to oligomeric and polymeric photoproducts. In contrast to the single-chain amphiphiles, photodimerization processes of lipoids containing two cinnamic acid moieties also occur in solution in organic solvents.

Lattice-controlled polyreactions

Lattice-controlled reactions leading to oligomers or polymers have been described for a variety of organic compounds¹⁻⁴⁾. Originally limited to solid state reactions only, the topochemically controlled photopolymerization of diacetylene containing lipid-like compounds (lipoids) has gained special interest recently⁵⁻¹⁰⁾. Because of their amphiphilic character these lipoids can be oriented into membrane-like structures such as monolayers, vesicles and multilayers. The topochemical polymerization of these oriented systems is packing dependent⁹⁾ and takes place on UV-irradiation to yield products which retain their membrane structure⁵⁻¹⁰⁾. The resulting polymeric membranes show some unique properties which make them valuable as stable models to mimic biomembrane processes, as compartmentalized organized systems or as planar stable, oriented membranes¹⁰⁻¹²⁾.

Cinnamic acid containing amphiphiles

The classical example of a topochemical reaction is the solid state photodimerization of cinnamic acid. This four-centre reaction is lattice controlled and leads to

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truxilic or truxinic acid depending on the crystal structure of the unsaturated acid¹³⁾. Polymers were not formed in crystal. In solution without any orientation control, the dimerization does not take place.

It was, thus, interesting to see which mechanisms can be applied to cinnamic acid derivatives of lipid structure. They can be organized in crystals as well as in membrane structures, eventually leading to different photoproducts as schematically presented in Fig. 1.

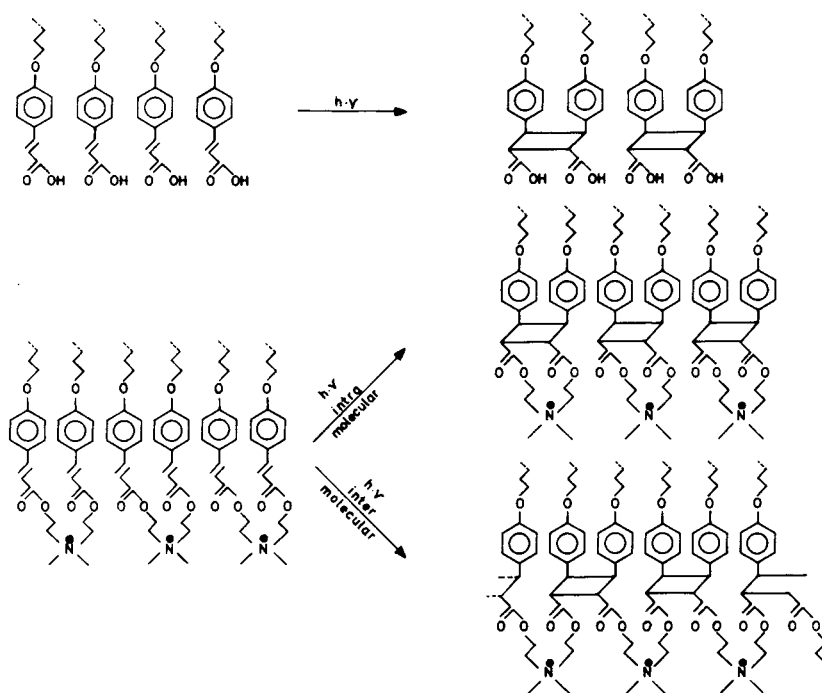
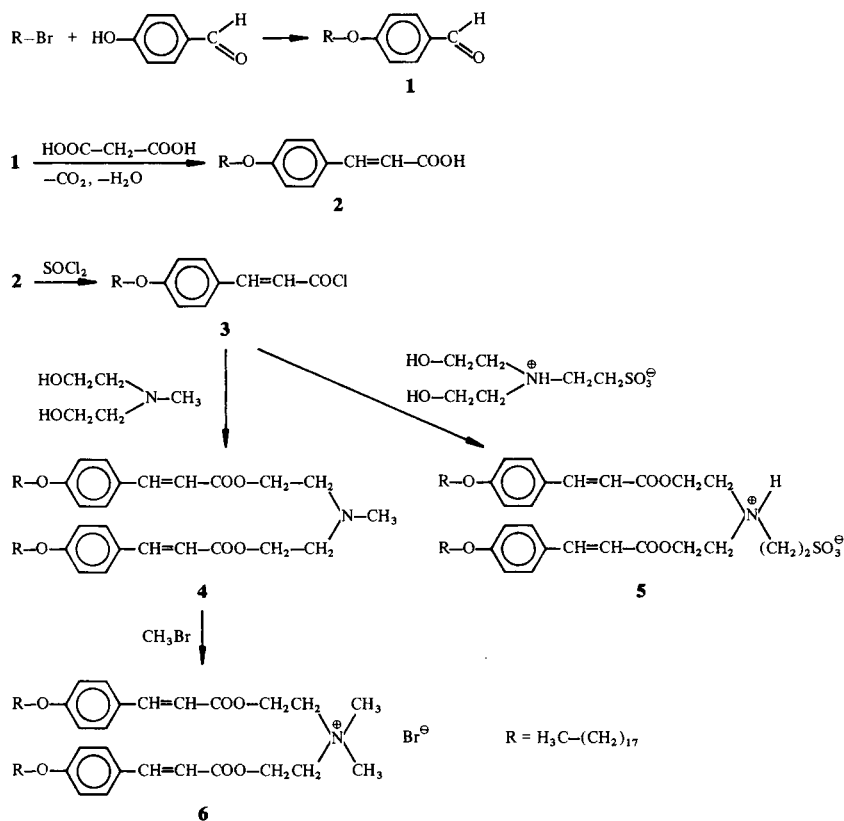


Fig. 1. Scheme of possible photodimerization reactions of single and double chain amphiphiles containing the cinnamic acid group

Single chain cinnamic acid amphiphiles^{14, 15)} are expected to yield photodimers with twice the molecular weight of the corresponding monomers. Double chain cinnamic acid lipoids can follow two reaction routes basically: they might react via an intramolecular dimerization without change of their molecular weight to yield bicycles, or alternatively via an intermolecular dimerization¹⁶⁾ to yield oligomeric or polymeric truxinic acid membranes.

For our investigation amphiphiles based on 4-octadecyloxyacetic acid with various polar head groups were used. Their synthesis is briefly summarized in the following reaction scheme:



In order to show that the photoreaction of the amphiphilic cinnamic acid derivatives follows the expected route, we first investigated the reaction in the crystalline state as well as in solutions of organic solvents. In addition, the photoreaction behaviour of these lipids was studied in monolayers and in liposomal dispersions. The two dimensional monomolecular layers at gas-water interfaces^{17, 18}, have been shown to be valuable model systems to investigate orientational effects on photoreactions^{9, 17, 18}. This technique allows to manipulate the orientation of amphiphilic compounds by a variation of the area occupied per molecule, which can be controlled by surface pressure, temperature and subphase¹⁸. The spherical vesicles (liposomes) are composed of one or more bilayer shells of lipids¹⁹ or synthetic lipids^{10, 20, 21}. Within the layers the lipids are two-dimensionally ordered. Their orientation is controlled by the temperature: below the phase transition temperature T_C the bilayers exist in a solid-analogue state above T_C in a liquid-analogue state.

Experimental part

General procedures: Solvents (acetone, chloroform, piperidine, pyridine) were dried and purified by passing through a column of basic alumina (Merck, activity I). All photoreactions were performed under nitrogen.

4-(Octadecyloxy)benzaldehyde (1): The compound was prepared from 4-hydroxybenzaldehyde and octadecyl bromide by a standard procedure²². The crude material was recrystallized from ethanol; m.p.: 51 °C.

$C_{25}H_{42}O_2$ (374,6)	Calc.	C 80,14	H 11,31
	Found	C 80,22	H 11,24

4-(Octadecyloxy)cinnamic acid (2): Aldehyde 1 was added to a solution of malonic acid (5,0 g; 48 mmol) in piperidine and the mixture was refluxed for 2 h. The solution was poured onto a mixture of 50 ml of conc. HCl and 100 g of ice and stirred until crystallization was complete (12 h). The crude material was filtered, washed with ethanol/ether and recrystallized twice from $CHCl_3$ /acetone (vol. ratio 2/1); colorless crystals with a smectic liquid crystalline phase: (k 121 s 148 i).

IR (KBr): 1678 (C=O), 1621 (C=C), 1172 (—C—O—C), 980 cm^{-1} ($(H) > C = C < H$, oop, *trans*-alkene).

¹H NMR ($CDCl_3$ /TMS): δ = 6,84–7,82 (m; 4H, ArH), 6,20–7,81 (d; 2H, vinyl protons of *trans*-alkene), 0,88 (t; 3H, CH_3 —), 1,26 (m; 32H, — CH_2 —), 3,99 (t; 2H, — CH_2 O—).

$C_{27}H_{44}O_3$ (416,6)	Calc.	C 77,84	H 10,64
	Found	C 77,61	H 10,75

4-(Octadecyloxy)cinnamoyl chloride (3): Acid 2 (4,16 g; 10 mmol) and freshly distilled $SOCl_2$ (2,0 g; 16,6 mmol) were heated for 2 h at 50 °C. The excess $SOCl_2$ was removed under reduced pressure. The pale yellow residue was used for further reactions without purification.

Bis[2-(4-octadecyloxy)cinnamoyl]ethylmethylamine (4): Acid chloride 3 (10 mmol) and *N*-methyl-diethanolamine (0,55 g; 4,61 mmol) were dissolved in $CHCl_3$ /pyridine (vol. ratio 10/1) and stirred for 48 h. The organic layer was then washed with 2 M HCl and water and dried over $MgSO_4$. After removal of the solvents under reduced pressure, the resulting material was recrystallized twice from acetone to give colorless crystals; m.p. 85–86 °C.

IR (KBr): 1708 (C=O), 1635 (C=C), 1176 (—C—O—C—) and 982 cm^{-1} ($(H) > C = C < H$, oop, *trans*-alkene).

¹H NMR ($CDCl_3$ /TMS): δ = 6,79–7,48 (m; 8H, Ar-H), 6,22–7,72 (2 d; 4H vinyl protons of *trans*-alkene), 0,88 (t; 6H, 1 CH_3 —), 1,25 (m; 64H, — CH_2 —) and 3,95 (m; 11H, — CH_2 —O, — CH_2 —N, N— CH_3).

$C_{59}H_{97}NO_6$ (916,4)	Calc.	C 77,31	H 10,67	N 1,53
	Found	C 77,20	H 10,81	N 1,64

Bis[2-(4-octadecyloxy)cinnamoyl]ethyl dimethylammonium bromide (6): The tertiary amine 4 (1,0 g; 1,09 mmol) was dissolved in $CHCl_3$ (80 ml) and cooled to 0 °C. After addition of CH_3Br (5 ml) the flask was sealed and the mixture stirred for 48 h at room temperature. The resulting precipitate was filtered off and recrystallized twice from ethanol. The compound forms colorless crystals; m.p. 130–131 °C.

IR (KBr): 1702 (C=O), 1640 (C=C), 1180 (—C—O—C—), 982 cm^{-1} ($(H) > C = C < H$, oop, *trans*-alkene).

$C_{60}H_{100}BrNO_6$ (1011,3)	Calc.	C 71,23	H 9,97	N 1,39
	Found	C 71,09	H 9,80	N 1,45

2-[Bis[2-(4-octadecyloxy)cinnamoyl]ethyl]amino]ethanesulfonic acid (5): Acid chloride 3 (2,9 g; 6,7 mmol) was dissolved in CHCl_3 /pyridine (60 ml/1 ml) and 2-[bis(2-hydroxyethyl)-amino]ethanesulfonic acid (0,66 g; 3,1 mmol) was added. The mixture was refluxed for 48 h. After addition of acetone (20 ml) the solution was cooled to room temperature. The crystallized product was filtered and recrystallized from CHCl_3 /acetone (vol. ratio 3/1) to give a colorless product; m. p. 240 °C.

IR (KBr): 1706 (C=O), 1640 (C=C), 1180 (—C—O—C—), 985 cm^{-1} ($\text{H} \text{>C=C<H}$, oop, *trans*-alkene).

^1H NMR (CDCl_3 /TMS): δ = 6,74–7,46 (m; 8H, Ar-H), 6,18–7,75 (2 d; 4H, vinyl protons of *trans*-alkene), 0,88 (t; 6H, CH_3), 1,27 (m; 64H, — CH_2 —), 3,95 (t; 4H, — CH_2 —O—), 3,74 (m; 6H, CH_2 —N— CH_2), and 4,58 (t; 4H, —COO— CH_2 —).

$\text{C}_{60}\text{H}_{99}\text{NO}_3\text{S}$ (1010,5)	Calc.	C 71,30	H 9,88	N 1,39	S 3,17
	Found	C 71,19	H 9,88	N 1,42	S 3,24

Photoreactions of amphiphilic cinnamic acid derivatives

In the crystalline state: To investigate the photoreaction in the crystalline state, microcrystalline suspensions of 2, 4, 5, and 6 in ethanol/water (vol. ratio 1 : 1) of 5 mg/ml were irradiated in quartz cuvettes with the unfiltered light of a high pressure Hg-Xe lamp. After 48 h of irradiation, the products were filtered and characterized via IR and UV spectroscopy, FD-mass spectrometry and size exclusion chromatography.

In monolayers: Spreading of monolayers of the amphiphilic cinnamic acid derivatives was performed on a Langmuir film balance (Lauda). The interfacial behaviour was characterized by recording the surface pressure-area (π/A) isotherms. The monolayers were irradiated under nitrogen at constant surface pressure by 254 nm UV-light of a low pressure mercury lamp (approximate power density 5 mW/cm²). The photoproducts were collected from the interface and their IR and UV spectra recorded.

In vesicles: Vesicles were prepared by ultrasonication using the microtip accessory of a Branson Model B-15 sonifier. Vesicles formation was proved by electron microscopy (Philips EM 300) and differential scanning calorimetry (Perkin Elmer DSC 2 C) Irradiation of vesicular dispersions was carried out as described for the microcrystalline suspensions.

In solution: To investigate the photoreaction of the cinnamic acid group in homogeneous solution the lipoids were dissolved in CHCl_3 or toluene (concentration 1 mg/ml) at room temperature. The isotropic solutions were irradiated as described for the microcrystalline suspensions.

Results and discussion

Photoreactions in microcrystalline suspensions

To be able to detect the influence of the close proximity of the cinnamic acid chains in the lipid monomers (4–6) the single chain lipid 4-octadecyloxy-cinnamic acid (2)^{14,15} was investigated first. The spectral changes found after 48 h or irradiation of the crystal suspension of 2 are summarized in Fig. 2 and compared with the corresponding spectra of the starting material.

After irradiation, the characteristic IR absorption bands of the monomer at 980 cm^{-1} (CH-deformation mode of *trans*-alkenes) and at 1630 cm^{-1} (C=O stretching mode) disappeared. In addition, the absorption at 1680 cm^{-1} (CO-conjugated stretching mode) is replaced by a band at 1700 cm^{-1} . Furthermore, the UV absorption maximum of the monomeric cinnamic acid derivative 2 (310 nm) vanished and a

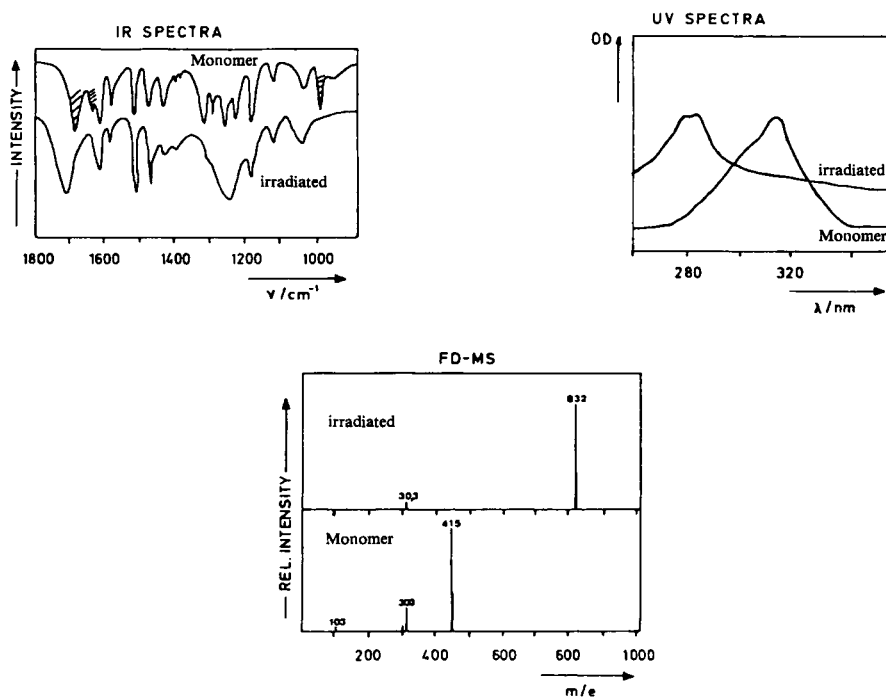


Fig. 2. Comparison of the IR spectra (KBr pellet), UV spectra (in CHCl_3) and the FD-MS spectra of monomer **2** and its photoproducts, obtained by irradiation in crystalline suspensions

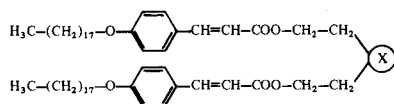
new maximum appeared at 280 nm. The spectral behavior of the photoproducts of **2** is directly comparable to that of the photodimers of free cinnamic acid. The photodimerization of monomer **2** is unambiguously demonstrated by the FD-mass spectrum of the photoproduct, which shows the $M + 2$ peak of the dimer as the only characteristic mass.

The double chain cinnamic acid derivatives **4**–**6** were investigated under analogous conditions. Their spectral data before and after irradiation are summarized in Tab. 1.

The IR and UV data in Tab. 1 show that the photoreactivities of **5** and **6** are remarkably higher than that of the free amine derivative **4**. The latter does not show any spectroscopic variation after 48 h of irradiation. This might be due to different crystal modifications of the two lipids which in case of **4** is unfavorable for the photo-reaction.

Under the experimental conditions, **5** and **6** are converted into photoproduct which show analogous spectral behavior as the single chain derivative **2**. Both IR-modes at 1635 and 982 cm^{-1} , which are characteristic for the CC double bond, are decreased or vanished, and a new band at 1730 cm^{-1} is formed. The new formed band corresponds to the isolated C=O stretching mode of the ester group. In agreement, the

Tab. 1. Spectral data of double chain cinnamic acid amphiphiles



before and after irradiation in crystal suspensions

Head group X	Irradiation time in h	IR (KBr) absorption maxima in cm ⁻¹ a)				UV absorption maxima in nm
		>C=O 1 730	>C=C-C=O 1 708	>C=C< 1 635	>C=C-H 982	
4:	—	—	+	+	+	310
	48	—	+	+	+	310
6:	—	—	+	+	+	317
	48	0	0	0	0	280, 317
5:	—	—	+	+	+	317
	48	+	—	—	—	280

a) + = strong absorption, 0 = weak absorption, — = no absorption.

monomer UV absorption peak at 317 nm is decreased or vanished and a new peak at 280 nm is exhibited. This points to a photodimerization reaction. Considering the extend of the decrease of the monomer IR and UV absorption bands, the photoreactivity of the lipoids increases with $4 < 5 < 6$.

To decide whether photodimerization is intra- or intermolecular, the products were characterized via size exclusion chromatography.

As demonstrated in Fig. 3, the photoproducts of **5** is not homogeneous with respect to its molecular weight. One compound is found with nearly the same retention-volume as the monomers pointing to the formation of an intramolecular dimer. But, in addition, high molecular weight components were detected at lower retention volumes. Whereas the peak at $V_e = 19$ ml can be attributed to dimers formed, the peak at $V_e = 16$ ml corresponds to the exclusion volume of the column. As the retention volume of polystyrene 2200 is $V_e = 17$ ml, this indicates the formation of oligomers and polymers. Thus, the photodimerization of **5** proceeds not only via an intramolecular reaction, but also via an intermolecular reaction leading to oligomeric and polymeric truxinic acid derivatives as schematically shown in Fig. 1.

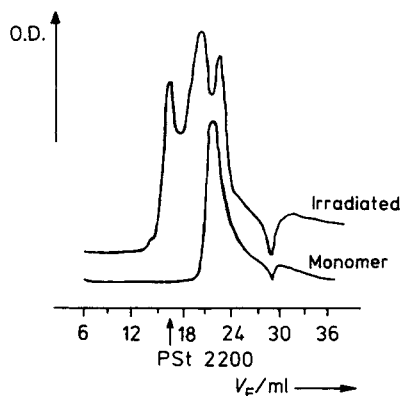


Fig. 3. Size exclusion chromatogram of monomer and irradiated 5. Micro Styragel (Waters) $2 \times 500 \text{ \AA} + 1 \times 100 \text{ \AA}$; solvent CH_2Cl_2 . PSt = polystyrene, molecular weight: 2200

Photoreaction monolayers

The amphiphiles **2** and **4–6** form monolayers when spread at the gas-water interface. Typical π/A isotherms are illustrated in Fig. 4. Within the temperature interval investigated ($0–45^\circ\text{C}$) all monomers are in the solid-analogue state. The collapse area of acid **2**, $22,5 \text{ \AA}^2 \cdot \text{molecule}^{-1}$, is similar to those of fatty acids ($18 \text{ \AA}^2 \cdot \text{molecule}^{-1}$)¹⁷. The double-chain amphiphiles **4–6** collapse at 45 to $50 \text{ \AA}^2 \cdot \text{molecule}^{-1}$, values close to those of natural lipids containing two long alkyl chains¹⁸. After UV irradiation the monomolecular film of acid **2** is slightly contracted from $22,5$ to $21,0 \text{ \AA}^2$ per molecule, and the collapse pressure π_c rises significantly from 28 to 40 mNm^{-1} . Both phenomena are well known in the photopolymerization of diacetylenes in monolayers and are interpreted in terms of a higher packing density and higher stability of the film^{24–26}.

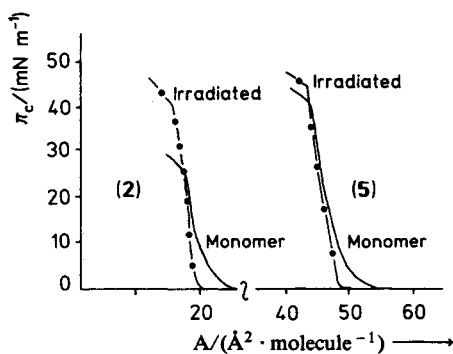


Fig. 4. Surface pressure area diagrams of monomer and irradiated **2** and **5**. $T = 20^\circ\text{C}$; subphase: water; pH 5,7

The photoproducts of **2** obtained from two-dimensional monolayers and three-dimensional crystals have identical spectra. Thus, the monomeric UV absorption maximum at 310 nm is replaced by an absorption maximum at 280 nm . In addition, the disappearance of the modes at 1630 and 980 cm^{-1} bands and the shift of the ester carbonyl bond peak from 1700 to 1730 cm^{-1} are observed. UV-irradiation of mono-

layers of the amphiphiles 4–6 results too in a contraction of the area occupied per molecule. In contrast to the acid 2, the π_c values of 4–6 do not increase significantly after the reaction (Fig. 4). After UV-irradiation, both the UV and IR spectra of compounds 4 to 6 change in the way described for compound 2. Prolonged irradiation of the monolayers results in photoproducts which UV spectra show absorption at shorter wavelengths, a result which may arise from photodegradation of the dimers. It has to be noted that compared to the crystalline state, the reactivity of the cinnamic acid group is much higher in monolayers. The same extents of conversion of acid 2 are achieved after 25 min of irradiation in monolayers, compared to 48 h of irradiation in crystal suspensions. The enhanced photoreactivity of the cinnamoyl derivatives in self-organized assemblies is demonstrated by the amine 4 as well, which is photosensitive only in monolayers, but not in the crystalline state. Concerning the reactivity in monolayers, there is no pronounced difference of the reaction rate of 4 to 6. As the packing density of the lipoids is nearly the same (approx. $23 \text{ \AA}^2 \cdot \text{molecule}^{-1}$), the similar arrangement of the reactive groups in the monolayer obviously results in similar reactivities.

Vesicles

Fig. 5 demonstrates the formation of spherical structures of the long-chain acid 2 with an average diameter of 300 nm. Because of the long hydrocarbon chains (C_{18}), vesicles composed of the single-chain acid 2 and the double-chain lipid 5 are characterized by high phase-transition temperatures. This is indicated by the DSC curves of lipid 5 in Fig. 6. The UV-spectral changes on irradiation of vesicles of 2 and 5 correspond closely to those observed in the crystalline state and in monolayers. On irradiation, the UV absorption maximum at 310 nm disappears and UV absorption maxima at 240 and 280 nm are formed. An electron micrograph of irradiated vesicles of 2, shown in Fig. 5, proves that the photoreaction of the cinnamic acid groups within the bilayer membrane takes place with retention of the spherical structure of the vesicles. Furthermore, DSC investigations of irradiated vesicular suspensions of lipid 5 indicate a disappearance of the phase transition after the polyreaction (Fig. 6). Similar phenomena were observed for the photopolymerization of diacetylene containing lipoids in bilayer membranes^{25, 26}.

Solution

Unlike the single-chain amphiphile 2, lipid-like compounds, containing two cinnamic acid groups, undergo intramolecular photodimerization in homogeneous solution. This behavior is comparable to photocrosslinking reactions of polymers containing the cinnamic acid group²⁷ and is probably a consequence of the high local concentration of the reactive moieties within the double chain molecule. In chloroform, a polar solvent, the dimerization is complete within 55 min of irradiation. In less polar solvents, such as toluene or mixtures of CHCl_3 /hexane, unreacted lipid is

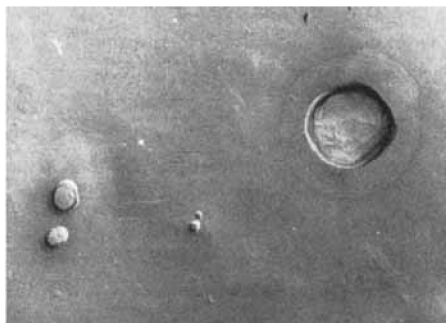


Fig. 5. a.

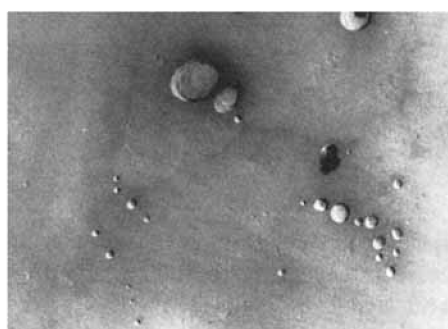


Fig. 5. b.

Fig. 5. Freeze fracture electron micrograph of vesicles of 2. (a): Monomer, (b): after 40 min UV-irradiation

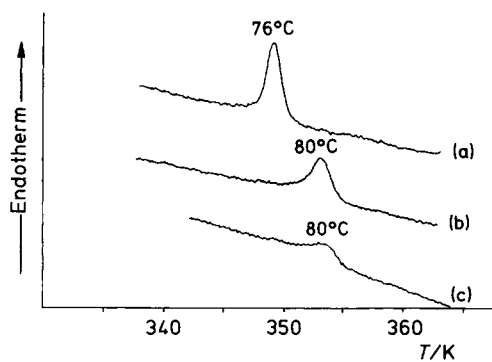


Fig. 6. DSC studies of the phase transition temperature of vesicles of 5. DSC (concentration 10 mg/ml) (a): Monomer, (b): after 20 min UV-irradiation, (c): after 40 min UV-irradiation

left after the same period of irradiation. The incomplete conversion of the monomers in nonpolar solvents might be explained by a better solubilization of the hydrocarbon chains and the cinnamic acid groups in these solvents. Thus, the reaction centers of the two hydrocarbon chains of the lipid molecule would be separated more efficiently by solvent molecules, and the reaction is retarded.

Conclusion

It was shown that in addition to the crystalline state, cinnamic acid derivatives can be reacted via photodimerization processes in oriented amphiphilic systems such as monolayers and liposomes. Furthermore, the photoreaction of these bifunctional amphiphilic cinnamic acid derivatives in solution demonstrates that the photoreaction is not restricted to topochemical, i. e. lattice controlled, conditions exclusively. If the distance between the cinnamic acid units is small enough the reaction will take place. The fast photodimerization of amphiphilic cinnamic acid derivatives in self-organized assemblies underlines the usefulness of this reactive moiety for monolayer and vesicle investigations. The photopolymerization of the double chain lipoids with two cinnamoyl groups via cyclobutane rings formed by intermolecular reactions was demonstrated, in addition to the intramolecular reaction which yields bicyclic photoproducts.

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