Rates of aminolysis were measured by following the appearance of the *p*-nitrophenoxide color. For the three model systems this was done by conventional spectroscopy and for the reaction of A–B with C–D, the stopped-flow method was used.

Table I shows the second-order rate constants for the rates between the neutral–neutral, positive–neutral, and neutral–negative reagents. For the reaction between the positive–negative reagents an equilibrium constant and a first-order rate constant as defined by eq 1 are shown.[12] Dividing the k_1 of the reaction of interest by the k_2 values for the three model reactions yields effective molarities of 4.5, 0.028, and 0.078 mol/L, respectively.

The use of three model reactions demonstrates that a simple two reaction comparison (uncharged reactants vs. oppositely charged reactants) would yield an EM which is too high. Even considering the two lower values, we do, however, obtain a fairly high effective molarity. It can be compared to the molarity of the solvent which is 11 M in dioxane and 0.56 M H_2O.[13] On the other hand, it does not compare to the often enormous proximity effects observed when the reactants are held together by a *covalent* bond.[14] Following Menger's recent conclusion[15] that "proximity effects manifest themselves in intramolecular reactions but *not* in intermolecular reactions" we would thus have to place juxtaposition by *one electrostatic bond* in the category of an intermolecular reaction. This conclusion may, of course, not necessarily apply to the cases of two or three point attachment found in enzyme binding and other biological recognition processes.

The ion-pair exchange equilibrium constant, K, which governs the formation of the reacting ion pair, $^-$A–B,$^+$C–D, and was found to have a value near unity, serves as a model for the internal equilibrium constants which enable an intermediary metabolite to move along a metabolic pathway.[16]

Acknowledgment. We thank Professor Richard Pizer of this department for help with the stopped-flow rate measurements and the PSC-CUNY Research Award Program of the City University of New York for support.

Registry No. $BF_4^-(CH_3)_3N^+(CH_2)_3CO_2$-*p*-$C_6H_4NO_2$, 109686-78-4; $CH_3(CH_2)_4CO_2$-*p*-$C_6H_4NO_2$, 956-75-2; $(n\text{-}C_4H_9)_4N^+{}^-O_3S(CH_2)_2NH_2$, 91900-05-9; $C_6H_5CH_2NH_2$, 100-46-9.

Supplementary Material Available: The equations and method used to calculate K and k_2 (5 pages). Ordering information is given on any current masthead page.

(12) The first-order rate expression, rate = k_1 [$^-$A–B,$^+$C–D] applies only at low amine concentrations, [A–B] < 10^{-4} M. At high amine concentrations, [A–B] > 10^{-2} the reaction follows second-order kinetics, rate = k_2[$^-$A–B,$^+$C–D][A–B], with a second molecule of amine assisting in proton removal from the tetrahedral intermediate. At intermediate amine concentration, a two-term rate expression is required, rate = k_1[$^-$A–B,$^+$C–D] + k_2[$^-$A–B,$^+$C–D][A–B].

(13) The solvent, 95.3 mol % dioxane–water, dielectric constant = 2.53, contains the least amount of water necessary to dissolve enough of the two charged reagents to prepare solutions for the kinetic runs ([AB] = 10^{-5} to 5×10^{-3} M, [C–D] = 10^{-5} to 5×10^{-5} M).

(14) An intramolecular reaction analogous to the reaction of A–B with C–D is the cyclization of *p*-nitrophenyl *N*-(2-aminophenyl)-*N*-methylcarbamate which has been estimated to have an EM ≥ 10^8 (Fife, T. H.; Hutchins, J. E. C.; Wang, M. S. *J. Am. Chem. Soc.* **1975**, *97*, 5878).

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Synthesis and Crystal Structures of Thioether-Strapped Porphyrins

Summary: Porphyrins containing a thioether linked by hydrocarbon chains and strapped from opposite corners of the macrocycle have been prepared and their structures determined crystallographically.

Sir: The active electron-transporting site of cytochrome *c* contains iron protoporphyrin IX coordinated axially by an imidazole (His-18) and a thioether (Met-80).[1] Attempts to prepare models for this system have been frustrated by the poorer ligand binding of thioethers to iron porphyrins compared with imidazoles. Indeed, only by covalently attaching either the imidzole[2-5] or the thioether[6-8] or both[9] to the porphyrin periphery can the unsymmetrical metalloporphyrin, Im-M-SR_2, be approached. The most successful model to date, the "tailed-imidazole" porphyrin of Mashiko et al.,[5] employs this strategy by covalent attachment of the imidazole to a tetraphenylporphyrin and use of an excess of the free thioether, tetrahydrothiophene. While the X-ray crystal structure of the ferrous derivative has been obtained, isolation of a ferric form has been complicated by head-to-tail dimerization, giving a mixture of six- and five-coordinate species. Herein we report the synthesis and X-ray crystal structures of a pair of novel porphyrins in which a thioether is constrained into a position above the porphyrin core by covalent attachment to diagonally opposite corners of the prophyrin macrocycle. For the longer chain compound **14a**, it was anticipated that the sulfur atom would be held in a favorable geometry for binding to a metal at the prophyrin core, while the shorter chain compound **14b** would demonstrate the effect of ring distortion on such metal–sulfur interaction.

In compound **14** the strap is sufficiently short that attachment to opposite corners of a preformed porphyrin will undoubtedly be impossible. Instead **14** was synthesized by a variation of the synthetic strategy previously reported for the preparation of strapped porphyrins.[10] This synthesis, which is outlined in Scheme I, is a general route for the preparation of strapped porphyrins bearing potential ligands in the strap. Because of the reactivity of the thioether, manipulation of the pyrrole α-methyl group must be carried out before the strap is set in place. Dimerization of the α-(free-iodoalkyl)pyrrole **8** using Na_2S to give compound **9** followed by reaction with the α-(chloromethyl)pyrrole **10** afforded the chain-linked bis(dipyrromethane) **11**. Deprotection and deesterification was followed by thermal decarboxylation to give the unstable **13** which was subjected to acid-catalyzed intramolecular cyclization under high dilution conditions to

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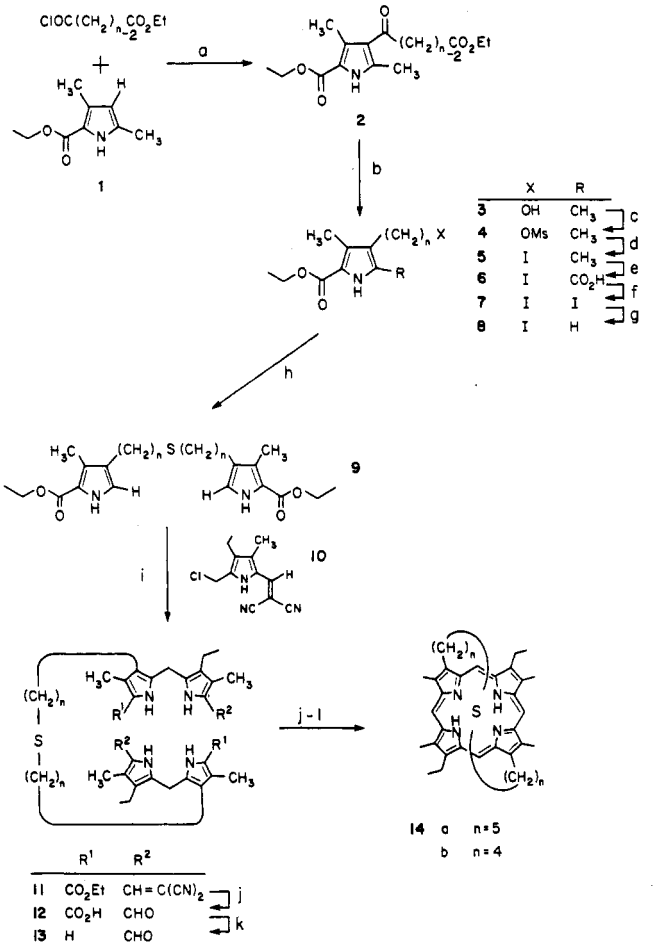
Scheme I



	yield, %	
	$n = 5$	$n = 4$
(a) $SnCl_4$, CH_2Cl_2, 0 °C	84	73
(b) $BF_3{\cdot}Et_2O$, $NaBH_4$, THF	85	72
(c) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C	92	88
(d) NaI, acetone, reflux	92	88
(e) SO_2Cl_2, CH_2Cl_2, Et_2O; H_2O, acetone, reflux	83	91
(f) $NaHCO_3$, KI, I_2, $ClCH_2CH_2Cl$, reflux	84	86
(g) HI, EtOH	88	43
(h) $Na_2S{\cdot}9H_2O$, H_2O, THF, reflux	97	94
(i) AcOH, 80 °C	84	90
(j) KOH, PrOH, H_2O, reflux		
(k) DMF, reflux	9–19	10–18
(l) TsOH, CH_2Cl_2, high dilution		

yield the strapped porphyrin **14** (n = 5, 9–19%; n = 4, 10–18% from **11**).[11] The porphyrins were found to be light-sensitive, with the preparation of both **14a** and **14b** being accompanied by varying amounts of the corresponding sulfoxides **15a** and **15b**. By analogy to the photooxidation of diethyl sulfide[12] and methionine,[13] it is believed that the free-base porphyrin acts as a photosensitizer to produce singlet oxygen which then oxidizes the thioether to the sulfoxide. This sulfoxide may be reduced back to the thioether in good yield (70–74%) by using methyltrichlorosilane/sodium iodide.[14]

(11) Satisfactory elemental analyses, mass spectra, and NMR spectra (^1H and ^{13}C) were obtained for all new compounds. Crystallographic data, full elemental analyses, and NMR and mass spectral data are available for compounds 1–14 in the supplementary material. See paragraph at end of paper.

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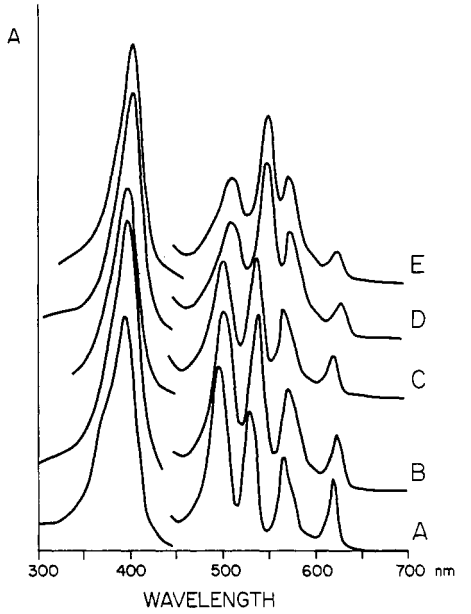

Figure 1. Optical spectra (CH_2Cl_2) of A, etioporphyrins II; B, **14a**; C, **14b**; D, **15a**; E, **15b**.

The optical spectra of the strapped porphyrins exhibited the expected features. Compared to the unstrained etioporphyrin II, introduction of the strap and consequent distortion of the porphyrin macrocycle results in a decrease in intensity of band IV relative to band III to give a Rhodo-type spectrum (Figure 1). This "Rhodofying" effect is more pronounced for the shorter C_4-thioether **14b**. Oxidation to the sulfoxide leads to a further decrease in intensity of band IV.

The most dramatic feature of the ^1H NMR spectra of the strapped porphyrins is the wide spread of the methylene resonances as the strap spans both the shielding and deshielding regions of the porphyrin diamagnetic ring current. The effect of this internal shift reagent allows identification of each resonance by simple decoupling experiments. A preliminary examination of the chemical shifts offered some insight into the conformation of the straps.

For the C_4-thioether **14b** the four protons adjacent to the sulfur occur at −3.74 ppm, suggesting that these protons are directed within the cavity bounded by the strap and the porphyrin, while the next adjacent protons occur further downfield at −0.86 and −0.62 ppm, indicating that these are directed outside the cavity. For the C_5-thioether **14a** the four protons adjacent to the sulfur occur at −2.02 and −1.56 ppm while the next adjacent four protons occur at −1.85 and −1.46 ppm. The crystal structure shows that the unit C–C–S–C–C is almost coplanar with one proton from each carbon directed within the cavity and the other on the outside.

Introduction of the strap and distortion of the porphyrin results in some disruption of the diamagnetic ring current. This is demonstrated by a reduced deshielding effect at the porphyrin periphery and upfield shifts of the methine protons and the methyls on rings 1 and 3. There was a corresponding downfield shift of the inner NH protons (**14a**, −3.38 ppm; **14b** −3.11 ppm) compared to etioporphyrin II (−3.76 ppm) due to diminished shielding at the porphyrin core.

These conclusions were supported by X-ray structure analysis. In the crystal structure of the C_5-thioether **14a**

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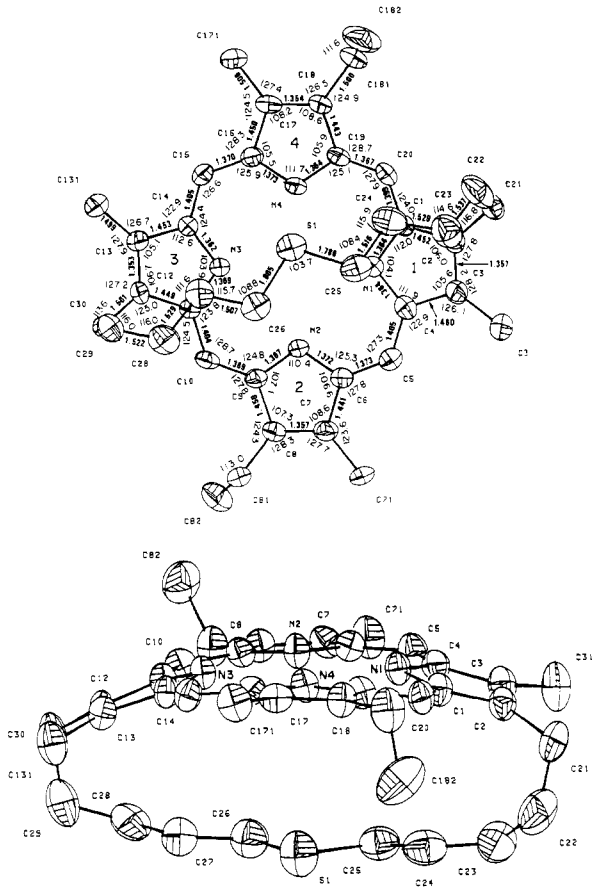

Figure 2. Thermal ellipsoid plot of the C_5-thioether **14a** (50% enclosure). Estimated standard deviations for C–C bond lengths are <0.017 Å and for angles <1.2°.

(Figure 2),[15] the angles between the mean planes in rings 1 and 3, and 2 and 4, are 143.3° and 174.5°, respectively. The crystal structure of the C_4-thioether **14b** (Figure 3)[16] contains two crystallographically distinct molecules. The first molecule (A) adopts a strap conformation in which the four protons adjacent to the sulfur are directed toward the cavity. This corresponds to the conformation existing in solution, as shown by ^{1}H NMR. The second molecule (B) is disordered. The major component [0.75 (1) occupation] adopts a conformation similar to that of the C_5-thioether **14a** in which the four carbons adjacent to the sulfur each have one proton directed within the cavity and one directed outside. The minor component has a strap

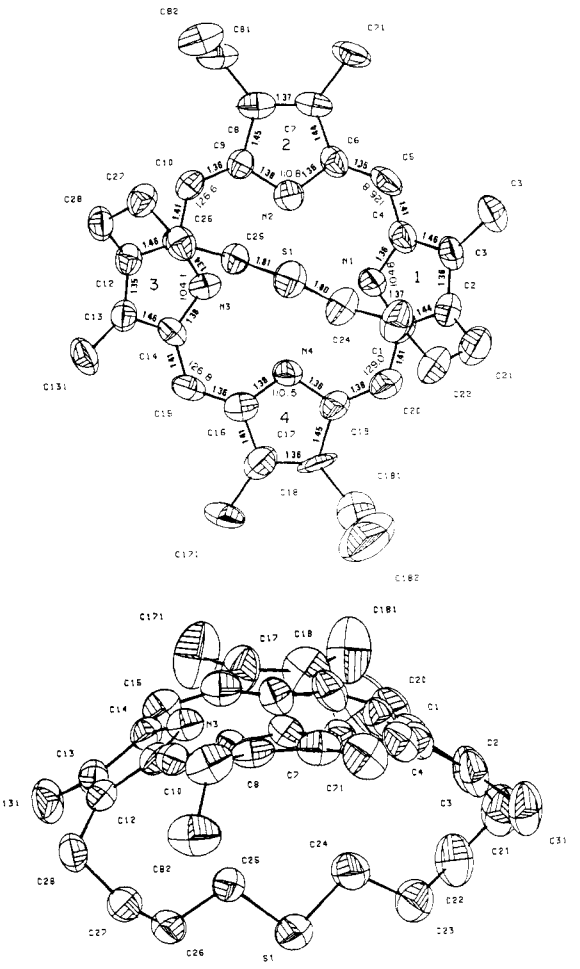

Figure 3. Thermal ellipsoid plot of the C_5-thioether **14b** (50% enclosure). Estimated standard deviations for C–C bond lengths are <0.010 Å and for angles <0.7°.

conformation as found in the first molecule (A). The porphyrin core differs between these two sets. For the two crystallographically distinct C_4-thioethers **14b** the angles between the mean planes in rings 1 and 3, and 2 and 4 are 115.6° (A), 159.3° (B) and 111.1° (A), 172.1° (B), respectively. The greater "doming" of the porphyrin nucleus in the shorter strap compound results in a consequent loss in aromaticity as shown by the downfield shift of the NH protons in the ^{1}H NMR spectra.

In general, the molecular dimensions of both compounds are comparable with previously determined structures.[19] However, while the differences in length between equivalent bonds are not statistically significant, it is interesting to note that they reflect a chemically reasonable decrease of aromaticity in both porphyrin skeletons.

Acknowledgment. This work was supported by the United States National Institute of Health (AM 17989) and the Canadian National Sciences and Engineering Research Council.

Registry No. **1**, 2199-44-2; **2a**, 68500-90-3; **2b**, 68500-89-0; **3a**, 98977-05-0; **3b**, 98977-04-9; **4a**, 98977-07-2; **4b**, 98977-06-1; **5a**, 98977-09-4; **5b**, 98977-08-3; **6a**, 98977-11-8; **6b**, 98977-10-7; **7a**, 98977-13-0; **7b**, 98977-12-9; **8a**, 98977-15-2; **8b**, 98977-14-1; **9a**, 110174-59-9; **9b**, 110174-63-5; **10**, 37789-74-5; **11a**, 110174-60-2; **11b**, 110174-64-6; **12a**, 110191-30-5; **12b**, 110174-65-7; **13a**, 110174-61-3; **13b**, 110174-66-8; **14a**, 110174-62-4; **14b**, 110174-67-9; **15a**, 110191-31-6; **15b**, 110174-68-0; ethyl hydrogen glutarate, 1070-62-8; ethyl succinyl chloride, 14794-31-1.

(15) Crystal data: $C_{38}H_{48}N_4S$, M = 592.9, monoclinic, space group $P2_1/n$, a = 13.910 (2), b = 14.396 (3), and c = 16.653 (3) Å, β = 92.69 (2)°, U = 3331 Å^3, Z = 4, D_c = 1.234 g cm^{-3}, μ(Mo K$_\alpha$) = 1.27 cm^{-1}, 4349 unique reflections were measured in the range ($0 < 2\theta \leq 45$) using graphite-monochromated Mo K$_\alpha$ radiation (λ = 0.71069 Å). The structure was solved by direct methods (MULTAN)[17] and refined by full matrix least squares (CRYSTALS)[18] using 2199 reflections with $\mathbf{I} > 3\sigma(I)$. The current R value is 0.052 (R_w = 0.057).

(16) Crystal data: $C_{36}H_{44}N_4S$, M = 564.8, monoclinic, space group $P2_1/n$, a = 10.696 (2), b = 21.849 (5), and c = 27.546 (8) Å, β = 93.89 (2)°, U = 6423 Å^3, Z = 8, D_c = 1.228 g cm^{-3}, μ(Mo K$_\alpha$) = 1.27 cm^{-1}, 5978 unique reflections were measured in the range ($0 < 2\theta \leq 40$) using graphite-monochromated Mo K$_\alpha$ radiation (λ = 0.71069 Å). The structure was solved by direct methods (MULTAN)[17] and refined by large block matrix least squares (CRYSTALS)[18] using 3274 reflections with $I > 3\sigma(I)$. In one of the independent molecules, disorder of the central $(CH_2)_2S(CH_2)_2$ portion of the strap was encountered and two orientations (of unequal occupancy) were refined with restraints being applied. The current R value is 0.071 (R_w = 0.072).

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Supplementary Material Available: Experimental procedures and elemental analyses, NMR and mass spectral data for compounds 1–14, and crystallographic data for compounds **14a** and **14b** (24 pages). Ordering information is given on any current masthead page.

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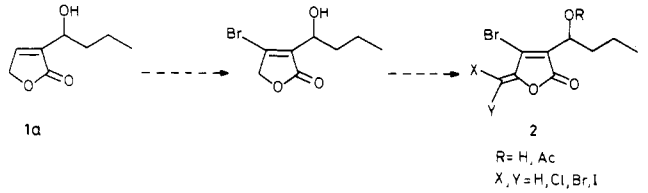
Received February 24, 1987

Synthesis of 3-(1-Hydroxyalkyl)furan-2(5*H*)-ones: Unexpected Substitution Reaction in Allylic Alcohols by Bromine

Summary: Substitution of an allylic hydroxyl group in α,β-butenolide derivatives by bromine under typical ionic bromination conditions is reported.

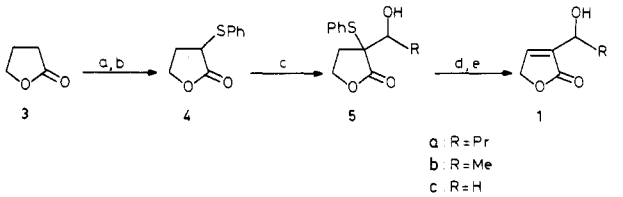
Sir: In relation to our research on structurally simple α,β-butenolides[1] we have prepared 3-(1-hydroxybutyl)-furan-2(5*H*)-one (**1a**) in order to study its bromination–dehydrobromination reactions, since the formed products could be possible intermediates for the synthesis of fimbrolides **2**.[2]



Product **1a** was already described,[3] but when the reported synthetic sequence was repeated, we found **1a** highly contaminated by the isomeric lactone 3-(1-hydroxybutyl)furan-2(3*H*)-one and by the dehydrated product, 3-(1-butenyl)furan-2(5*H*)-one. Therefore, we conceived a new synthesis starting from commerical butyrolactone **3** (Scheme I).

B. M. Trost et al. had synthesized **1b** by another route since they found that the anion generation of **4** followed by quenching with aldehydes led to equivocal results.[4] On the other hand, Hoye and co-workers[5] described better results for these condensations when performed in the presence of $ZnCl_2$. We allowed the reaction of the anion of 3-(phenylthio)-4,5-dihydrofuran-2(3*H*)-one[6] (**4**) with butyraldehyde to proceed in the absence of Lewis catalysts. Thus, **5a** was isolated as a 1:1 diastereoisomeric mixture in 84% yield;[7] both isomers were separated by column chromatography (mp 66–68 and 81–82 °C). Oxidation of

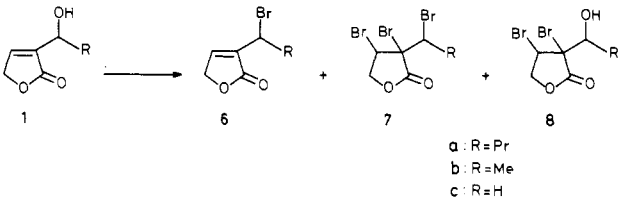
Scheme I



(a) Br_2; (b) PhSNa, THF; (c) LDA, RCHO; (d) *m*-CPBA or $NaIO_4$; (e) pyrolysis.

crude **5a** with *m*-chloroperbenzoic acid in methylene chloride at 0 °C for 1 h or with sodium periodate in methanol/water (1:1) at room temperature for 17 h, followed by pyrolysis of the corresponding sulfoxides, afforded **1a** in 65–80% yield.

When **1a** was submitted to the conventional ionic bromination conditions (1 equiv of puriss. bromine, purchased from Fluka AG, in CCl_4), to our surprise, we isolated the new 3-(1-bromobutyl)furan-2(5*H*)-one (**6a**), which results from the substitution of the hydroxyl group by the bromine atom leaving the double bond unmodified. Changing the conditions of the reaction (solvent, time; entries 1–4 of Table I) never did give rise to an addition reaction on **1a**.



The structural assignment of **6a** was unambiguous since the IR spectrum presented no absorption in the 3600–3050 cm^{-1} (OH region), the ^1H NMR spectrum showed a broad singlet at δ 7.47 (vinylic proton), and the chemical ionization (NH_3) mass spectrum indicated molecular ions at *m/e* 238, 236 $(C_8H_{11}BrO_2 + 18)^+$.

Note from Table I that starting material **1a** was always recovered in fair yields and that when the reaction time was highly prolonged the tribromo derivative **7a** (correct mass spectrum) was isolated in 14% yield, indicating its formation from **6a**. This was confirmed by independent bromination of **6a** (entries 7 and 8).

Due to this unexpected reaction behavior we decided to study in more detail this bromination process. The only described substitution reactions of the OH group for bromine are, to the best of our knowledge, the cases of 3-phenyl-2-propen-1-ol and 1-phenyl-2-propen-1-ol, in which the tribromo derivatives were obtained in poor yields.[8,9] No explanation for these results was given. Moreover, the mechanism of molecular bromine addition to olefines[10] and the halogenation of α,β-unsaturated acyclic esters[11] have received much attention during recent years. In addition, the bromination of the **6a** analogous compound, 3-butylfuran-2(5*H*)-one, takes place under standard reaction conditions yielding the normal addition product.[12]

In order to study the influence of the alkyl chain we synthesized **1b**[4] and **1c** (IR ($CHCl_3$) 3650–3300 cm^{-1}; ^1H

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