A “trimethyl lock” system has been known to facilitate lactonization reactions through what has been termed a steroepopulation control mechanism. We have found that a similar trimethyl lock system can also facilitate cyclic ether formation with the concomitant release of a carboxylic acid in the presence of anhydrous tetrabutylammonium fluoride. To study this base-mediated trimethyl lock-facilitated cyclic ether formation, we synthesized fifteen model compounds. All model compounds underwent base-mediated cyclic ether formation in high yields at 0 °C to room temperature (r.t.) with the concomitant release of the attached carboxylate. Such a system potentially could be used for the development of a two-dimensional linker for solid phase peptide and organic synthesis.

Key words “trimethyl lock”; cyclization; linker; fluoride; quinone; hydroquinone

A “trimethyl lock” system has been known to facilitate lactonization reactions and cyclic ether formation in aqueous solutions. The mechanism through which such a trimethyl lock facilitates certain cyclization reactions has been thought to be due to the conformational restrictions imposed by the trimethyl lock (Chart 1). Such trimethyl lock-facilitated lactonization reactions have been used to develop redox-, esterase-, and phosphatase-sensitive prodrugs and redox-sensitive protecting groups for amines. In our studies of such trimethyl lock-facilitated cyclization reactions, we have found that facile base-mediated cyclic ether formation can be also accomplished at room temperature (r.t.) through treatment of the open-chain system with tetrabutylammonium fluoride (TBAF) (Chart 1).

Recently, there has been a great deal of interest in developing linkers that are stable during synthetic reactions yet readily cleavable under mild reaction conditions for solid phase synthesis. Conceivably, this cyclization system could be used for the development of a two-dimensional linker for solid phase peptide and organic synthesis. In such a design, the quinone ester moiety could be attached to an appropriate solid phase material, and the carboxylic acid moiety could be either a protected amino acid for solid phase peptide synthesis or another organic acid, which would be modified through solid phase reactions. Such a linker, if successfully developed, would have the advantages of being cleavable with a mild reducing agent, such as Na2S2O4, and TBAF, and of being more stable under acidic conditions than the commonly used benzyl ester linker. In addition, many amino acid side chain protections are expected to be stable under the cleavage conditions. Therefore, this type of resin linker will be particularly suitable for the synthesis of large peptides and small proteins using segment synthesis methods. The final cleavage is a two-step process: reduction followed by treatment with TBAF. This helps to minimize the stability problems of this linker during any single chemical transformation.

To study the feasibility of such a system for the development of a novel two-dimensional linker for solid phase synthesis, we synthesized a series of esters of acids with different structural features. These acids included protected amino acids and simple aliphatic and aromatic carboxylic acids. The cyclic ether formation with the concomitant release of the acid was studied after the reduction of the quinone moiety to the hydroquinone (Chart 1). We have found that such cyclizations could be accomplished with esters of acids with a variety of different structural features, indicating the general applicability of such a system in the development of a novel linker for solid phase synthesis.

Results and Discussion

For 1 to be used as a potential solid phase linker for peptide and organic syntheses, it was necessary to test the cyclization reactions of esters 2 with different structural features. First, we were interested in studying the cyclic ether formation of 2 with protected amino acids attached to the quinone moiety. Among the twenty natural amino acids, we chose nine representative ones (Chart 2). This group in-
cluded amino acids bearing non-polar side chains (2a—e), aromatic side chains (2a, e), and protected side chain functional groups such as hydroxyl (2h), thiol (2g), amino (2i), and carboxyl groups (2f). We also synthesized the esters of several other carboxylic acids with different structural features. Compounds 2j—m, and o are all esters of aliphatic carboxylic acids with different steric hindrances and functional groups, and compound 2n is an ester of an aromatic carboxylic acid.

Synthesis The synthesis of these esters 2 started with lactone 5. The hydroxyl group of 5 was first protected as a benzyl ether to give 6, which was then reduced using LiAlH₄ (LAH) to give the diol 7 (Chart 2). It is known that without the benzyl protection of the phenol hydroxyl group, the reduction reaction is very slow due to the negative charge of the phenoxide. Our initial plan was to oxidize the phenol 7 to quinone 9 (Chart 3), which would be followed by acylation of the primary hydroxyl group to give the desired products 1. However, this approach did not lead to the formation of the desired product. Similar quinones in the presence of a trimethyl lock are known to undergo cyclizations to give a mixture of the spiroether 10 and a hemiketal 11, which makes the acylation of the hydroxyl group of quinone 9 impossible. Therefore, we studied the feasibility of selective acylation of the primary hydroxyl group of the diol intermediate 7 for the preparation of the desired product 1. The selective acylation of the primary hydroxyl group of 7 was easily accomplished in high yields (about 90%) when the acids were protected amino acids (8a—i) activated with either dicyclohexylcarbodiimide (DCC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC). Presumably due to the steric hindrance presented by the gem-dimethyl groups of 7 and the relative steric bulkiness of protected amino acids, the esterification occurred almost exclusively on the primary hydroxyl group to give the desired products 8 (Table 1).

Other acids bearing α-substituents also gave high yields of the monoester. Such was the case for 8k, o. However, acids that did not have an α-substituent tended to give the diester as the side product. Such was the case for 8j, m, and n. For 2,2-dimethylpropanoic acid (8l), the reaction using DCC as the activating agent was very slow, presumably because of the steric hindrance imposed by the tert-butyl group. Therefore, N,N-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (Bop-Cl) was used for the preparation of this compound (8l) in 67% yield. Oxalyl chloride was used as the activating reagent for the preparation of 8n, o. The diester side product was found for the preparation of 8n, which was the reason for the relatively low yield (73%).

For subsequent model studies, the hydroquinone was first
It suggests that peptides synthesized on this linker could probably be cleaved at 0°C, whereas organic compounds could only be released from the solid phase at r.t.

It should be noted that TBAF is a very commonly used reagent, most notably for the cleavage of silyl protecting groups, and is known not to compromise the chiral integrity of protected amino acids, peptides, and other organic compounds. However, we did not specifically examine the issue of racemization in this study. In a separate study, we have attached this linker to polystyrene resin beads. This linker was used for the successful synthesis of two short peptides [Boc–Trp–Ala–Gly–Gly–OH and Boc–Asn–Ala–Ser(OBn)–Gly–Glu(OBn)–OH], further demonstrating the utility of such a linker system. However, because of the potential NBS oxidation problems associated with sulfur-containing amino acids, the application of this linker for the synthesis of peptides with the first amino acid being either protected cysteine or methionine may be problematic.

Table 1. Reaction Yields

<table>
<thead>
<tr>
<th>RCO</th>
<th>Formation of 1</th>
<th>Final release</th>
</tr>
</thead>
<tbody>
<tr>
<td>a  Boc–Phe</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>b  Boc–Leu</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>c  Boc–Gly</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>d  Boc–Ala</td>
<td>93</td>
<td>91</td>
</tr>
<tr>
<td>e  Boc–N-formyl–Trp</td>
<td>93</td>
<td>100 (80)</td>
</tr>
<tr>
<td>f  Boc–β-OBn–Asp</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>g  Boc–S–Bn–Cys</td>
<td>93</td>
<td>73</td>
</tr>
<tr>
<td>h  Boc–O–Bn–Ser</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>i  Boc–ε-Cbz–Lys</td>
<td>85</td>
<td>99</td>
</tr>
<tr>
<td>j  COCH(C(=O)C6H5)2</td>
<td>72</td>
<td>99</td>
</tr>
<tr>
<td>k  COCH(CH3)2</td>
<td>89</td>
<td>95</td>
</tr>
<tr>
<td>l  COCH(C6H5)2</td>
<td>67</td>
<td>96</td>
</tr>
<tr>
<td>m  COCH2C6H5</td>
<td>80</td>
<td>96</td>
</tr>
<tr>
<td>n  CO–C10H7</td>
<td>73</td>
<td>98</td>
</tr>
<tr>
<td>o  (+)-COCH(CH3)–C10H6–6-OMe</td>
<td>91</td>
<td>99</td>
</tr>
</tbody>
</table>

a) Yields for the formation of 1 and 8 were isolated yields. Yields for the final release were determined by HPLC, except for the yields in parentheses, which were isolated yields.

collapsed to the corresponding quinone compound 1 through oxidation with N-bromosuccinimide (NBS). The yields for this step of the reaction were generally close to quantitative, except for 8g, the cysteine ester. It was suspected that the oxidation of the sulfur atom by NBS was the reason for this low yield. However, no detailed study was carried out to characterize the side product(s) from this oxidation reaction.

Final Cleavage The reduction of the quinone 1 to hydroquinone 2 was accomplished by shaking an ether solution of the quinone ester (1a–o) and an aqueous solution of Na2S2O4 at r.t. The reaction color quickly changed from yellow to almost colorless, indicating the completion of the reduction. Approximately 20-fold Na2S2O4 was employed. The yields were almost quantitative. The cyclization reaction was carried out by treatment of 2 with 1 M TBAF/tetrahydrofuran (THF) solution. These cyclization reactions were studied using reversed-phase HPLC by monitoring both the formation of the cyclic ether 3 and the disappearance of the starting material 2. The formation of the acid 4 was also monitored when the acid had a chromophore. Figure 1 shows a typical HPLC reaction profile.

The quantitation of these compounds was carried out using the corresponding standard curves. The yields of these reactions were generally very high (Table 1). For two compounds (2e, o), the isolated yields were determined (Table 1). It should be noted that the cyclization was usually accompanied by a color change from yellow to orange and finally to blue/green. For the esters of protected amino acids, the cyclization was carried out at 0°C under a nitrogen atmosphere with a TBAF/ester ratio of 3/1. However, the same reaction for the esters of the other carboxylic acids (2j–n) did not occur at 0°C; instead, the reactions were carried out at r.t. It should also be noted that for these non-amino acid esters, the reactions were carried out with a ratio of TBAF/ester of 8/1. Low reaction temperature (0°C) and a lower ratio of TBAF/ester (3/1) led to lower yields. This indicated that the carboxylic acid moiety does influence the cyclization reaction. This is particularly relevant for the proper design of the reaction conditions in solid phase organic/peptide synthesis.
(13.17 g, 59.9 mmol), benzyl chloride (15.16 g, 120 mmol), K2CO3 (16.52 g, 120 mmol), NaI (0.5 g, 13 mmol) and 120 ml of acetone (dried on molecular sieves, 4 Å) were mixed in a flask. The reaction mixture was refluxed for 20 h. Acetone was evaporated and the residue was dried with 100 ml of water. This was extracted with methylene chloride (2×100 ml). The combined CH2Cl2 layers were washed with 100 ml of water and dried over MgSO4. The filtrate was treated according to the general procedure (Method B) to give a white foam (186 mg, 99%).

To Boc–Phe–OH (1.224 g, 4.62 mmol) and DMAP (24 mg, 0.2 mmol) were treated according to the general procedure (Method B) to give a white foam (136 mg, 99%).

H-NMR (CDCl3) δ 7.51—7.26 (m, 5H), 6.40 (s, 2H), 4.12 (t, J = 6.9 Hz, 2H), 3.70 (d, J = 5.7 Hz, 2H), 2.44 (s, 3H), 2.33 (t, J = 6.9 Hz, 2H), 2.20 (s, 3H), 1.56 (s, 6H), 1.45 (s, 9H).

IR (film) 3377, 1736, 1713, 1689, 1499, 1452, 1400, 1377, 1319, 130.9, 129.22, 128.59, 127.93, 114.29, 29.82, 16.81, 16.27, 16.22; IR (film) 3377, 1737, 1716, 1689, 1499, 1452, 1400, 1377, 1218, 1148 cm−1; FAB-MS m/z: 485 (M+) .

Anal. Calc. for C19H20N2O3: C, 76.76; H, 7.53; N, 2.54.

Diol-Trp Ester 8e: Diol 7 (126 mg, 0.4 mmol), Boc–Trp(For)-OH (266 mg, 0.8 mmol), EDC (154 mg, 0.8 mmol) and DMAP (24 mg, 0.2 mmol) were treated according to the general procedure (Method B). The reaction afforded a white foam (182 mg, 94%).

H-NMR (CDCl3) δ 7.47—7.32 (m, 3H), 6.41 (s, 2H), 4.68 (s, 2H), 4.14 (t, J = 7.2 Hz, 2H), 4.05 (m, 1H), 2.44 (s, 3H), 2.21 (m, 2H), 2.18 (s, 3H), 1.57, 1.55 (2s, 6H), 1.45 (s, 9H), 1.27 (d, J = 6.8 Hz, 3H).


Diol-Asp Ester 8f: Diol 7 (126 mg, 0.4 mmol), Boc–Asp(OBn)–OH (258 mg, 0.8 mmol) and DMAP (24 mg, 0.2 mmol) were treated according to the general procedure (Method B). The reaction afforded a white foam (234 mg, 93%).

H-NMR (CDCl3) δ 8.93, 8.60 (2s, 1H), 5.16—4.78 (m, 10H), 4.44, 4.38 (d, 2H, J = 6.1 Hz), 3.98, 3.87 (t, 2H, J = 6.1 Hz), 3.76 (m, 10H), 2.74, 2.69 (t, 2H, J = 6.8 Hz, 2H), 2.43 (s, 3H), 2.19 (m, 2H), 1.54, 1.52 (2s, 6H), 1.44 (s, 9H), FAB-MS m/z 628 (M+) .

Anal. Calc. for C34H43NO6: C, 70.67; H, 7.50; N, 2.46. Found: C, 70.51; H, 7.22; N, 4.43.

Diol-Propion Ester 8j: Diol 7 (126 mg, 0.4 mmol), Boc–Prop(OBn)–OH (258 mg, 0.8 mmol), EDC (154 mg, 0.8 mmol) and DMAP (24 mg, 0.2 mmol) were treated according to the general procedure (Method B). The reaction afforded a white foam (193 mg, 92%).

H-NMR (CDCl3) δ 7.47—7.32 (m, 3H), 6.41 (s, 2H), 4.68 (s, 2H), 4.14 (t, J = 7.2 Hz, 2H), 4.05 (m, 1H), 2.44 (s, 3H), 2.21 (m, 2H), 2.18 (s, 3H), 1.57, 1.55 (2s, 6H), 1.45 (s, 9H), 1.27 (d, J = 6.8 Hz, 3H).

was evaporated. The residue was separated on a silica gel column (ethyl acetate: hexane = 1:4) to give 8i (114 mg, 67%) as a white solid: 1H-NMR (CDCl3) δ 7.40 (m, 5H), 6.37 (s, 1H), 4.69 (s, 2H), 0.0.00 (t, J = 7.2 Hz, 2H), 2.45 (s, 3H), 2.28 (t, J = 7.2 Hz, 2H), 2.15 (s, 3H), 1.59 (s, 6H), 1.15 (s, 9H); FAB-MS m/z 398 (M+). Anal. Calc. for C21H31NO6: C, 64.10; H, 7.94; N, 3.56. Found: C, 64.24; H, 7.93; N, 3.61.

Quinone-Trp Ester 1e: Diol-ester 8e (124 mg, 0.256 mmol) was treated with NBS (45 mg, 0.256 mmol) according to the general procedure to give 1f (98 mg, 97%) as a yellow oil: 1H-NMR (CDCl3) δ 6.48 (m, 1H), 4.23 (m, 2H), 0.49 (m, 2H), 2.20 (s, 3H), 2.00 (d, J = 1.2 Hz, 3H). 1H-NMR (CDCl3) δ 189.48, 188.28, 187.14, 159.48, 153.21, 150.73, 144.18, 142.15, 135.16, 126.65, 125.47, 124.03, 123.45, 119.37, 111.74, 109.11, 80.23, 63.44, 50.11, 39.93, 38.95, 38.78, 28.32, 28.31, 15.59, 14.81; IR (film) 1736, 1712, 1645, 1508, 1453, 1366, 1244, 1166 cm−1; FAB-MS m/z 393 (M+). Anal. Calc. for C35H40N2O5: C, 73.61; H, 7.19; N, 5.22. Found: C, 73.67; H, 7.18; N, 5.28.

Quinone-Cys Ester 1g: Diol-ester 8g (119 mg, 0.196 mmol) was treated with NBS (35 mg, 0.196 mmol) according to the general procedure to give 1h (60 mg, 73%) as a yellow oil: 1H-NMR (CDCl3) δ 7.30 (m, 5H), 6.46 (s, 1H), 4.43 (m, 4H), 4.07 (m, 2H), 3.79 (s, 3H), 2.99 (2H), 2.39 (s, 3H), 1.99 (s, 3H), 1.45 (s, 9H), 1.42 (s, 6H); 1H-NMR (CDCl3) δ 189.47, 188.35, 187.13, 152.65, 150.84, 148.12, 148.10, 142.15, 135.59, 127.35, 127.18, 80.05, 63.11, 54.67, 41.00, 39.43, 38.58, 30.29, 28.48, 15.57, 14.78; IR (film) 3150, 1714, 1648, 1488, 1366, 1166 cm−1; FAB-MS m/z 515 (M+). Anal. Calc. for C40H43N2O5S: C, 65.22; H, 7.23; N, 2.72. Found: C, 65.28; H, 7.35; N, 2.98.

Quinone-Ser Ester 1h: Diol-ester 8h (118 mg, 0.200 mmol) was treated with NBS (36 mg, 0.200 mmol) according to the general procedure to give 1i (50 mg, 95%) as a yellow oil: 1H-NMR (CDCl3) δ 7.30 (m, 5H), 6.46 (s, 1H), 4.50 (m, 2H), 4.35 (m, 1H), 4.09 (m, 2H), 3.79—3.63 (m, 2H), 2.19 (2H), 2.17 (s, 3H), 1.99 (s, 3H), 1.44 (s, 9H), 1.41 (s, 6H); 1H-NMR (CDCl3) δ 189.47, 188.35, 187.14, 152.65, 150.84, 148.12, 148.10, 142.15, 135.59, 127.35, 127.18, 80.05, 63.11, 54.67, 41.00, 39.43, 38.58, 30.29, 28.48, 15.57, 14.78; IR (film) 3150, 1714, 1648, 1488, 1366, 1166 cm−1; FAB-MS m/z 515 (M+). Anal. Calc. for C40H43N2O5S: C, 65.22; H, 7.23; N, 2.72. Found: C, 65.28; H, 7.35; N, 2.98.
Quinone-Propionic Ester
Quinone-methylnaphthaleneacetic Ester

Quinone-Trimethylacetic Ester

Quinone-Naphthoic Ester

Quinone-6-methoxy-Boc-indole-formyl-tryptophan

Quinone-102

Quinone-45

Quinone-189

Quinone-188

Quinone-187

Quinone-184

Quinone-183

Quinone-182

Quinone-181

Quinone-180

Quinone-179

Quinone-178

Quinone-177

Quinone-176

Quinone-175

Quinone-174

Quinone-173

Quinone-172

Quinone-171

Quinone-170

Quinone-169

Quinone-168

Quinone-167

Quinone-166

Quinone-165

Quinone-164

Quinone-163

Quinone-162

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Quinone-15

Quinone-14

Quinone-13

Quinone-12

Quinone-11

Quinone-10

Quinone-9

Quinone-8

Quinone-7

Quinone-6

Quinone-5

Quinone-4

Quinone-3

Quinone-2

Quinone-1

Quinone-0

References and Notes
1) Atilan Zheng and Daxian Shan made equal contributions to this paper.
     e) Danforth C., Nicholson A. W., James J. C., Loudon G. M., ibid., 98, 4275 — 4280 (1976);


