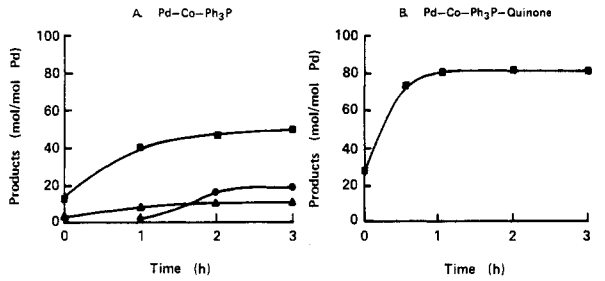

Figure 1. Effect of catalytic 1,4-benzoquinone on the products of the reaction of carbon monoxide, oxygen, and methanol over a palladium(II) acetate, cobalt(II) acetate, and triphenylphosphine catalyst: dimethyl oxalate (■), dimethyl carbonate (▲), and methyl formate (●). A 300-mL stainless steel autoclave was charged with $Pd(OAc)_2$ (0.50 mmol), Ph_3P (1.51 mmol), $Co(OAc)_2 \cdot 4H_2O$ (2.00 mmol), methanol (500 mmol), diglyme (10.03 mmol), and methylene chloride to give 100 mL of solution. 1B also contains 1,4-benzoquinone (2.50 mmol). After being flushed with nitrogen, the autoclave was further charged with 1250 psi of carbon monoxide and 75 psi of oxygen and heated with rapid stirring to 90 °C. Products were withdrawn periodically and analyzed by gas chromatography using diglyme as an internal standard. Time zero is defined as the time the reactor reached 90 °C. For each 30 mmol of product, an additional charge of carbon monoxide (75 psi) and oxygen (25 psi) was added to the reactor.

reaction with oxygen. Often these systems are considerably less selective than either the stoichiometric conversion or the previously described system with quinone oxidant and triphenylphosphine-modified palladium(II) acetate catalyst. Part of this loss in selectivity has been blamed on the presence of water,[1,10] a coproduct, and part is due to the known catalytic activity of some of the most effective cocatalysts (e.g., Cu) for the formation of carbonate esters under oxalate-forming conditions.[11] Additionally, the metals most commonly employed [e.g., Cu(II) and Fe(III)] are one-electron oxidants while the palladium oxidation state, by analogy to the stoichiometric reaction, is presumably changing by two electrons.

A large number of cobalt–Schiff base complexes are known to form complexes with oxygen[12] and in some cases have been reported to be oxidation catalysts (e.g., phenol to benzoquinone).[13] Several of these complexes were examined as oxidation cocatalysts in the oxalate synthesis as it was felt that their mechanism of action would be different from that of simple copper or iron salts.[14] Although they do serve as cocatalysts for oxalate formation from carbon monoxide, oxygen, and alcohol, it was found that their behavior is not substantially different from that observed for cobalt(II) acetate, suggesting that the Schiff base oxygen complexes are not a factor. Product formation with time is shown for the palladium(II) acetate, cobalt(II) acetate, and triphenylphosphine (1:3:4 mole ratio) catalyst system in Figure 1A. Although the selectivity for oxalate formation is moderately high for the first hour of reaction, both selectivity and activity drop substantially between 1 and 3 h. The product formation with time shown for this cobalt cocatalyst is not substantially different from that reported for several other systems.[14]

However, a significant improvement in the catalytic oxalate synthesis results from the addition of catalytic amounts of 1,4-benzoquinone to the palladium(II) acetate, cobalt(II) acetate, and triphenylphosphine catalyst. Substantial improvements in the reaction rate, selectivity, and conversion are noted. The rate of product formation with time for the quinone-containing catalyst is shown in Figure 1B. A 3- to 4-fold increase in initial rate is observed over the system with no quinone, and the total amount of oxalate per palladium increases by almost a factor of 2. Most importantly, no more than trace amounts of either carbonate or formate esters are observed. With strongly coordinating solvents such as acetonitrile, as many as 140 mol of dimethyl oxalate can be obtained per mole of palladium before catalyst activity is lost.[14] At least part of the activity can be restored by the addition of more triphenylphosphine. Other ligands more stable to oxidation and less reactive toward quinones have been tried, but none have been found that give the high selectivity of the phosphine-containing catalyst.

In summary, the addition of benzoquinone has been shown to have an important, but as yet unexplained, effect on the initial rate, conversion, and selectivity for the palladium-catalyzed formation of oxalate esters. Similar improvements in the catalyst lifetime require the discovery of a catalyst as selective as phosphine-modified palladium(II) acetate but more stable to deactivation by oxidation.

Registry No. $(Ph_3P)_2Pd(OAc)_2$, 14588-08-0; $Pd(OAc)_2$, 3375-31-3; $Co(OAc)_2$, 71-48-7; PPh_3, 603-35-0; 1,4-benzoquinone, 106-51-4; methanol, 67-56-1; dimethyl oxalate, 553-90-2.

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Received January 25, 1983

(10) (a) Zehner, L. R. U.S. Patent 3 992 436, 1976. (b) Zehner, L. R. *Ibid.* 4 005 131, 1977. (c) Zehner, L. R.; Zajacek, J. G. *Ibid.* 4 041 067, 1977. (d) Zehner, L. R.; Zajacek, J. G. *Ibid.* 4 041 068, 1977. (e) Zehner, L. R. *Ibid.* 4 065 490, 1977. (f) Zehner, L. R. *Ibid.* 4 069 388, 1978.
(11) Romano, U.; Tessei, R.; Mauri, M. M.; Rebora, P. *Ind. Eng. Chem. Prod. Res. Dev.* **1980**, *19*, 396.
(12) Jones, R. D.; Summerville, D. A.; Basolo, F. *Chem. Rev.* **1979**, *79*, 139.
(13) Hutchings, D. A. U.S. Patent 3 859 317, 1975.
(14) Current, S. P. U.S. Patent 4 281 174, 1981.

Novel Use of Crown Ethers in Chemical Ionization Mass Spectrometry[1]

Summary: Chemical ionization mass spectra of a sample compound S mixed with a crown ether C display abundant $(C + H + S)^+$ ions through selective adduct ion formation when S is an amino acid, purine, pyrimidine, amide, or some other N–H-containing compound.

Sir: Crown ethers[2,3] are characterized by a cavity of a particular size ringed by a number of ether oxygens that complex with cations. The size of the cavity determines which cation would undergo efficient complexation.[4] In the course of a study by chemical ionization mass spectrometry (CIMS) on possible crown ether complexation in the gas phase, we have made several interesting observations.

(1) Mass Spectral Studies. Part 13. For Part 12, see: Bose, A. K.; Pramanik, B. N.; Bartner, P. L. *J. Org. Chem.* **1982**, *47*, 4008.
(2) Goldberg, I. "The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and their Sulphur Analogues", Supplement E1; Patai, S., Ed., Wiley: London, 1981.
(3) For recent reviews on the complexing properties of crown ethers, see: (a) *Top. Curr. Chem.* **1981**, 98. (b) De Jong, F.; Reinhoudt, D. N. *Adv. Phys. Org. Chem.* **1980**, *17*, 279.
(4) Thus, 12-crown-4 binds Li^+ strongly, but for efficient binding of the larger ions Na^+ and K^+, 18-crown-6 has to be used. Potassium acetate, which is insoluble in benzene, can be dissolved in that solvent upon the addition of 18-crown-6. The K^+ ion is complexed with all six oxygen atoms and is held inside the cavity ("in the nest" position) while the acetate serves as the gegenion.

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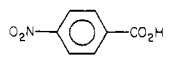
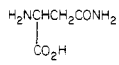
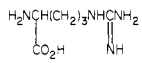
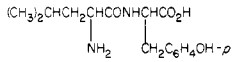
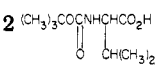
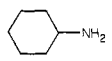
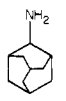
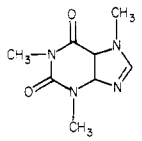
Table I. Chemical Ionization Mass Spectra with Crown Ether as Reagent

analyte[a]	reagent[b]	positive ions observed[c]
1 CH_3CO_2K	A	$(M + 1)$, $(M + 19)$[d]
2 NaI	A	$(M + 1)$, $(M + 19)$
3 $H_2NCH(CH_3)CO_2H$	B	$(M + 1)$, $(M + 1 + S)$
4 CH_3CONH_2	B	$(M + 1)$, $(M + 1 + S)$
5 $C_4H_9OC_4H_9$	A	$(S + 1)$ w, $(M + 1)$, $(M + 19)$
6 $PhCONHCH_2CO_2H$	A	$(S + 1)$ w, $(M + 1)$, $(M + 19)$, $(M + 1 + S)$ w
7 	A	$(S + 1)$, $(S + 18)$, $(M + 1)$, $(M + 19)$, $(2S + 1)$
8 $H_2NCH_2CO_2H$	A	$(M + 1)$, $(M + 19)$, $(M + 1 + S)$ s
9 	B	$(S + 1)$ w, $(M + 1)$, $(M + 1 + S)$ w
10 	A	$(S + 1)$ w, $(M + 1)$, $(M + 19)$, $(M + 1 + S)$ w
11 	B	$(M + 1)$, $(M + 1 + S)$
12 	A	$(M + 1)$, $(M + 19)$, $(M + 1 + S)$ w
13 	B	$(S + 1)$ w, $(M + 1)$ w, $(M + 1 + S)$
14 $[CH_3(CH_2)_6]_2NH$	A	$(M + 1)$, $(M + 19)$, $(M + 1 + S)$ s
15 $CH_3CH_2CH_2CH_2OH$	A	$(M + 1)$, $(M + 19)$, $(M + 1 + S)$ traces
16 	A	$(M + 1)$, $(M + 19)$, $(M + 1 + S)$
17 	A	$(M + 1)$, $(M + 19)$, $(M + 1 + S)$

[a] The analyte was mixed intimately with the reagent by grinding roughly equal proportions of the two together. Analytes: (1) potassium acetate, (2) sodium iodide, (3) alanine, (4) acetamide, (5) dibutyl ether, (6) *N*-benzoylglycine, (7) *p*-nitrobenzoic acid, (8) glycine, (9) asparagine, (10) arginine, (11) L-leucyl-L-tyrosine, (12) *N*-Boc-valine, (13) cyclohexylamine, (14) diheptylamine, (15) 1-butanol, (16) adamantylamine, (17) caffeine. [b] A = 18-crown-6; B = 12-crown-4. [c] The *m/z* 200–600 range was scanned by using methane as the reagent gas; the probe was unheated and not in the "in-beam" position; the ion source was at about 180 °C and under 1 torr of pressure. *M* and *S* designate the molecular weights of the crown ether and the analyte, respectively: A, $M = 264$; B, $M = 176$. The strong peaks are marked s and weak peaks w. [d] Crown ethers absorb moisture readily; the $(M + 19)^+$ peak corresponds to $(M + H_3O)^+$. This peak can be minimzed but not completely eliminated by using freshly distilled crown ether.

Expecting to find $(M + K)^+$ ions in the mass spectrum, we introduced a mixture of 18-crown-6 and potassium acetate into a CI mass spectrometer[5] via a solids probe. But we failed to observe any intense ions other than $(M + 1)^+$ and $(M + 19)^+$ where *M* corresponds to the molecular weight of the crown ether used; in some cases a cluster ion $(2M + 1)^+$ appeared after a few minutes. On the other hand, when an amino acid such as glycine or alanine was mixed with 18-crown-6, the CI mass spectra showed an intense peak for the ion $(M + S + 1)^+$ where *S* corresponds to the amino acid molecular weight. Under parallel conditions, however, alcohols, phenols, and ketones produced no noticeable adduct ion peaks in the mass spectrum.

Representative compounds of various types that produced adduct ion CI mass spectra with crown ethers are shown in Table I. It may be noted that amino acids, peptides, *N*-acyl amino acids, and even tertiary amines produce abundant adduct ions.

Recently X-ray crystallographic structure determination has established[6,7] that amino compounds can form complexes with crown ethers through hydrogen bonding with the ether oxygens. Even active methylene compounds such as acetonitrile, malononitrile, and nitromethane form crystalline complexes with 18-crown-6.[7]

In the light of these facts, we can easily rationalize our observations: amino compounds must form such strong hydrogen bonds with crown ether oxygen atoms that the adduct travels through the mass spectrometer under vacuum at 180 °C without dissociation and thus generates intense $(M + 1 + S)^+$ ions. We have observed that when an equimolar mixture of 18-crown-6 and 12-crown-4 is used with acetamide, the adduct with the former is much more abundant than the adduct with the latter—this too can be rationalized by noting that 18-crown-6 has 50% more sites for hydrogen bonding than 12-crown-4.

In case of a tertiary amine (for example, *N*-methylmorpholine) it can be assumed that formation of a quaternary ammonium ion by protonation permits strong

(5) Chemical ionization mass spectra were recorded by the direct-probe technique using a Biospect spectrometer (Scientific Research Instruments Corp., Baltimore, MD), operated at 1.1 kV under about 1 torr of methane. The probe was unheated; the ion source was heated to 190–200 °C.

(6) Harkema, S.; Van Hummel, G. J.; Daasvaln, K.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Comm.* **1981**, 368.

(7) de Boar, J. A. A.; Reinhoudt, D. N.; Harkema, S.; Van Hummel, G. J.; De Jong, F., *J. Am. Chem. Soc.* **1982**, *104*, 4073.

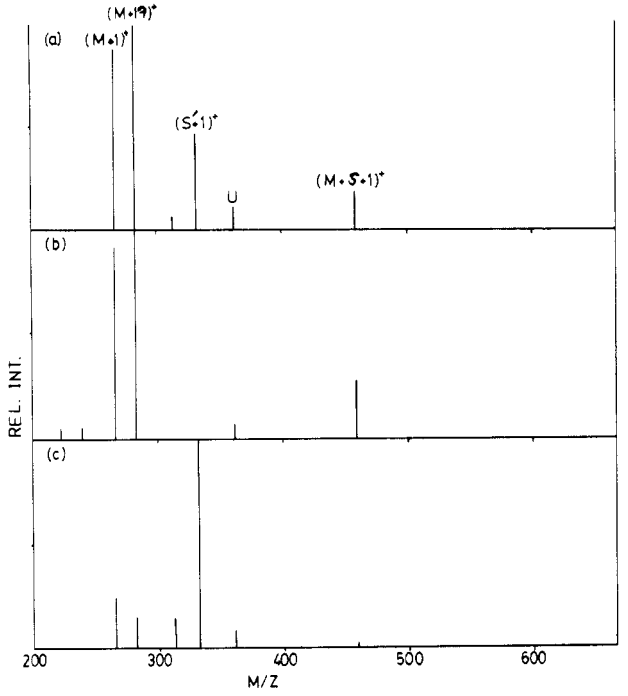


Figure 1. CIMS (CH_4) of a mixture of freeze-dried coffee, 18-crown-6, and 11α-hydroxyprogesterone: (a), (b), and (c) are three successive scans as the temperature of the ion source was raised from ~170 to 190 °C; the molecular weight of caffeine = S = 194, 18-crown-6 = M = 264; 11α-hydroxyprogesterone = S' = 330. An unidentified peak is marked U. Note the absence of the adduct ion at m/z 595 corresponding to the sterol.

hydrogen bonding between the amino nitrogen and the ether oxygens. The more intense adduct ions from amines compared to alcohols may perhaps be ascribed to the larger number of available hydrogens in the former for complexation with crown ether oxygens. In any case, this difference in binding—whatever be the underlying reason—could be of practical value for selective analysis of amino compounds in the presence of alcohols, ketones, esters, etc.

As an illustration of the selectivity achieved by using crown ethers, we cite an experiment in which commercial freeze-dried coffee mixed with a sterol was the analyte and 18-crown-6 was the reagent; at m/z >200 an adduct ion for caffeine was observed at m/z 459 but no adduct ion for the sterol or other compounds was displayed except possibly for one unidentified peak (see Figure 1).

It is significant that biologically important purines and pyrimidines such as adenine and cytidine produce intense adduct ions. We plan to explore the possibility of using crown ethers for easy detection of unusual bases from nucleic acids. The analysis of amino acids, dipeptides, and other amino acid derivatives by forming crown ether adducts is also under study.

Acknowledgment. We are grateful to Stevens Institute of Technology and the Office of Naval Research (N00014-83-C-0233) for the support of this research and the Schering–Plough Foundation for a generous grant for the chemical ionization mass spectrometry facility. We thank Provost R. Cotellessa, Dr. F. T. Jones, and A. Attridge for their interest and support.

Registry No. 1, 127-08-2; 2, 7681-82-5; 3, 56-41-7; 4, 60-35-5; 5, 142-96-1; 6, 495-69-2; 7, 62-23-7; 8, 56-40-6; 9, 70-47-3; 10, 74-79-3; 11, 968-21-8; 12, 13734-41-3; 13, 108-91-8; 14, 2470-68-0; 15, 71-36-3; 16, 13074-39-0; 17, 58-08-2; 18-crown-6, 17455-13-9; 12-crown-4, 294-93-9; methane, 74-82-8.

(8) Visiting Scholar from Zhejiang University supported by the People's Republic of China and Stevens Institute of Technology.
(9) Present addess: Mount Sinai School of Medicine, Department of Psychiatry, New York, NY, 10029.

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A New Entry to Highly Functionalized Perhydroindans via Free Radical Cyclizations

Summary: Reductive alkylation of substituted benzoic acids followed by iodolactonization and free radical cyclization provides an efficient stereoselective route to *trans*-perhydroindans.

Sir: Free radical carbon–carbon bond-forming addition reactions are attracting renewed attention from synthetic organic chemists.[1-3] We have recently examined a route to fused carbocycles in which a radical cyclization plays a crucial role.[4] This report described the initial results of this study and in particular documents a promising new entry to highly functionalized perhydroindans.

We began our studies by examining the reaction sequence outlined in Scheme I. Birch reduction of *m*-toluic acid (1) followed by alkylation of the resulting dianion with 4-bromo-1-butene afforded acid **2** (91%),[5] which was converted to iodo lactone **3** ($NaHCO_3$–H_2O–Et_2O) in a 61% yield.[6,7] Treatment of **3** with tri-*n*-butyltin hydride and AIBN in benzene under reflux gave a separable mixture of isomeric lactones **5**, **6**, **7**, and **8** (87%; 1:12:2:6) presumably via cyclization of radical **4**.[8] The structures of **5**, **7**,[9]

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(2) For recent carbocycle syntheses via intramolecular radical cyclizations, see: Bakuzis, P.; Campos, O. O. S.; Bakuzis, M. L. F. *J. Org. Chem.* **1976**, *41*, 3261. Buchi, G.; Wüest, H. *Ibid.* **1979**, *44*, 546. Stork, G.; Baine, N. H. *J. Am. Chem. Soc.* **1982**, *104*, 2321. Danishefsky, S.; Chackalamannil, S.; Uang, B.-J. *J. Org. Chem.* **1982**, *47*, 2231.
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(4) For relevant reviews, see: Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073 and references cited therein.
(5) Van Bekkum, H.; Van Den Bosch, C. B.; Van Minnenpathius, G.; De Mos, J. C.; Van Wijk, A. M. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 137.
(6) For a review, see: Staninets, V. I.; Shilov, E. A. *Russ. Chem. Rev. (Engl. Transl.)* **1971**, *40*, 272.
(7) For halolactonization of 1,4-dihydrobenzoic acids, see: Barnett, W. E.; Needham, L. L. *J. Org. Chem.* **1975**, *40*, 2843. Holbert, G. W.; Weiss, L. B.; Ganem, B. *Tetrahedron Lett.* **1976**, 4435. Bromolactonization of **2** afforded a mixture of β-and γ-lactones.
(8) Pure samples of **5**–**8** were obtained by GLC. From a preparative standpoint, lactone **6** (mp 106–107 °C) was crystallized directly from the product mixture in a 39% yield.
(9) The stereochemical details of **7** and the minor perhydroindans obtained in the cyclizations of **12**, **17**, and **23** are unknown. We suspect, however, that they are merely the C(7) isomers of the major perhydroindans.

0022-3263/83/1948-1782$01.50/0