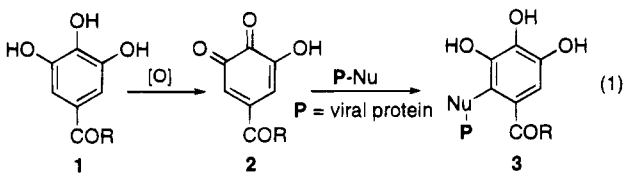
Chemistry of Galloyl-Derived *o*-Quinones: Reactivity toward Nucleophiles

Stéphane Quideau,[†] Ken S. Feldman,*[,†] and Heidi M. Appel[‡]

Department of Chemistry and Pesticide Research Laboratory, The Pennsylvania State University, University Park, Pennsylvania 16802

Received May 31, 1995

Gallotannins are higher plant secondary metabolites composed of a carbohydrate core, typically β-D-glucopyranose, to which either gallic acid or oligomers of depsidically-linked gallic acids are esterified.[1] The inherent affinity of these polyphenols for proteins render it plausible that (1) they contribute to the chemical defense of plants against pathogenic microbes and herbivores *via* protein-binding and enzyme inactivation,[1a,2] and (2) they may also play an important role in limiting the infectivity of viral pathogens against insect herbivores.[3] In particular, oak gallotannins reduce the infectivity of naturally occurring nuclear polyhedrosis viruses in gypsy moth caterpillars.[3] The molecular mechanism(s) of this inhibition is far from clear, but an intriguing hypothesis built on the observations that the larval midgut is highly basic (pH = 8–11)[4] and very oxidizing (E_h = +200–250 mV)[4] has been proposed.[2a] Thus, it is possible that these chemical conditions are conducive to oxidative activation of the polyphenolic substrates to furnish reactive, electrophilic *o*-quinones which can then covalently trap nucleophilic sites on viral proteins and mediate reduction of infectivity, eq 1, R = β-D-glucopyranose. A study aimed



1 2 3 (1)

at modeling the chemistry of these putative covalent interactions between gallotannins and viral proteins has been initiated. This information may ultimately impact on the design and selection of more efficient microbial pesticides for controlling plant predation by insect herbivores.[5]

Conjugate and/or direct addition of various heteroatom-nucleophiles to simple *o*-quinones has been extensively investigated because of the relevancy of this reaction type to many biological processes,[6] but galloyl-derived *o*-quinones have received little attention. This communication reports preliminary results concerning the reactivity profile of galloyl-derived *o*-quinones in addition reactions with representative nucleophiles such as amino acids and organometallic reagents.

The readily available *o*-quinones **4** and **5** (see supporting information) were exposed to amine- and thiol-based nucleophiles. The biologically relevant nucleophile models lysine and cysteine were chosen based upon literature precedents which implicate lysyl and cystyl residues as possible primary sites of protein attachment to catechol-derived quinones.[7] All reactions were performed by slowly adding a 0.05–0.1 M solution of quinone in THF to an equimolar 0.05–0.1 M solution of nucleophile in THF or THF:H_2O in order to minimize subsequent oxidation of initial adducts by unreacted *o*-quinones which may yield further potent electrophilic *o*-quinones. Selected examples of successful nucleophilic capture of both **4** and **5** are shown in Scheme 1. Thiophenol gave rise to the rearomatized adducts **6** and **7**[8] as the sole regioisomers shown in 47% and 69% yields, respectively. Similarly, addition of cysteine[7g,9] to both **4** and **5** in ca. 4:1 THF–H_2O delivered the 2-*S*-cysteinylgallate derivatives **8** and **9**,[8] respectively, in 67% and 62% yields. Hydrogenolysis of **9** cleanly furnished the fully deprotected 2-(*S*-cysteinyl)gallic acid **10** (Scheme 1).

This successful addition of thiol-based nucleophiles is in marked contrast to the case of lysine which, under the same conditions, did not react with **5**. Addition of N^{α}-(carbobenzyloxy)lysine to **4**, performed in alkaline me-

[†] Department of Chemistry.
[‡] Pesticide Research Laboratory.

(1) (a) Haslam, E. *Plants Polyphenols - Vegetable tannins revisited*; Cambridge University Press: Cambridge, 1989. (b) Gross, G. In *Plant Polyphenols. Synthesis, Properties, Significance*; Hemingway, R. W., Laks, P. E., Eds.; Plenum Press: New York, 1992; pp 43–60.

(2) (a) Appel, H. M. *J. Chem. Ecol.* **1993**, *19*, 1521 and references cited therein. (b) Luck, G.; Liao, H.; Murray, N. J.; Grimmer, H. R.; Warminsky, E. E.; Williamson, M. P.; Lilley, T. H.; Haslam, E. *Phytochemistry* **1994**, *37*, 357. (c) Scalbert, A. *Phytochemistry* **1991**, *30*, 3875. (d) Hagerman, A. E.; Buttler, L. G. In *Herbivores, Their Interaction with Secondary Metabolites*; Rosenthal, G. A., Berenhaum, M. R., Eds.; Academic Press: San Diego, 1991; Vol. 1; pp 355–388. (e) Spencer, C. M.; Cai, Y.; Martin, R.; Gaffney, S. H.; Goulding, P. N.; Magnolato, D.; Lilley, T. H.; Haslam, E. *Phytochemistry* **1988**, *27*, 2397. (f) Mole, S.; Waterman, P. G. *Phytochemistry* **1987**, *26*, 99.

(3) (a) Schultz, J. C.; Hunter, M. D.; Appel, H. M. In *Plant Polyphenols. Synthesis, Properties, Significance*; Hemingway, R. W., Laks, P. E., Eds.; Plenum Press: New York, 1992; pp 621–637. (b) Schultz, J. C.; Keating, S. T. In *Microbial Mediation of Plant-Herbivore Interactions*; Barbosa, P., Krischik, V. A., Jones, C. G., Eds.; Wiley: New York, 1991; Vol. 16, pp 489–506.

(4) (a) Appel, H. M.; Maines, L. W. *J. Insect Physiol.* **1995**, *41*, 241. (b) Schultz, J. C.; Lechowicz, M. J. *Oecologia* **1986**, *71*, 153.

(5) Appel, H. M. In *Insect-Plant Interactions*; Bernays, E. A., Ed.; CRC Press: Boca Raton, 1994; Vol. V, pp 209–223.

(6) (a) Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*; Wiley: New York, 1988; Vol. 2, Parts 1 and 2. (b) Kutyrev, A. A. *Tetrahedron* **1991**, *47*, 8043. (c) Monks, T. J.; Hanzlik, R. P.; Cohen, G. M.; Ross, D.; Graham, D. G. *Toxicol. Appl. Pharmacol.* **1992**, *112*, 2. (d) Peter, M. G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 555.

(7) (a) Hanzlik, R. P.; Harriman, S. P.; Frauenhoff, M. M. *Chem. Res. Toxicol.* **1994**, *7*, 177. (b) Nakano, H.; Tahara, S.; Iizuka, T.; Mizutani, J. *Agric. Biol. Chem.* **1987**, *51*, 549. (c) Matheis, G.; Whitaker, J. R. *J. Food Biochem.* **1984**, *8*, 137. (d) Pierpoint, W. S. In *Leaf Protein Concentrates*; Telek, L., Graham, H. D., Eds.; AVI: Westport, Connecticut, 1983; pp 235–267. (e) Mason, H. S.; Peterson, E. W. *Biochim. Biophys. Acta* **1965**, *111*, 134. (f) Felton, G. W.; Duffey, S. S. *J. Chem. Ecol.* **1990**, *16*, 1221. (g) Sugumaran, M.; Dali, H.; Semensi, V. *Arch. Insect Biochem. Physiol.* **1989**, *11*, 127. (h) Kalyanaraman, B.; Premovic, P. I.; Sealy, R. C. *J. Biol. Chem.* **1987**, *262*, 11080.

(8) The regiochemistry of nucleophilic attack was unambiguously determined by a combination of HMBC and NOESY or delayed COSY NMR experiments; see Supporting Information.

(9) (a) Prota, G.; Scherillo, G.; Nicolaus, R. A. *Gazz. Chim. Ital.* **1968**, *98*, 495. (b) Ito, S.; Prota, G. *Experientia* **1985**, *41*, 960. (c) Salgues, M.; Cheynier, V.; Gunata, Z.; Wylde, R. *J. Food Sci.* **1986**, *51*, 1191. (d) Tse, D. C. S.; McCreery, R. L.; Adams, R. N. *J. Med. Chem.* **1976**, *19*, 37. (e) Hanzlik, R. P.; Weller, P. E.; Desai, J.; Zheng, J.; Hall, L. R.; Slaughter, D. E. *J. Org. Chem.* **1990**, *55*, 2736. (f) Richard, F. C.; Goupy, P. M.; Nicolas, J. J.; Lacombe, J.-M.; Pavia, A. A. *J. Agric. Food Chem.* **1991**, *39*, 841. (g) Cilliers, J. J. L.; Singleton, V. L. *J. Agric. Food Chem.* **1990**, *38*, 1789. (g) Sanada, H.; Suzue, R.; Nakashima, Y.; Kawada, S. *Biochim. Biophys. Acta* **1972**, *261*, 258. (h) Dudley, E. D.; Hotchkiss, J. H. *J. Food Biochem.* **1989**, *13*, 65. (i) Tanaka, T.; Fujisaki, H.; Nonaka, G.; Nishioka, I. *Heterocycles* **1992**, 33, 375.

(10) (a) Davies, R.; Frahn, J. L. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2295 and references cited therein. (b) Cranwell, P. A.; Haworth, R. D. *Tetrahedron* **1971**, *27*, 1831.

(11) Alcoholic solvents have been reported to favor conjugate addition of aniline to *o*-quinones: (a) Tindale, C. R. *Aust. J. Chem.* **1984**, *37*, 611. (b) Horspool, W. M.; Smith, P. I.; Tedder, J. M. *J. Chem. Soc. (C)* **1971**, 138. Such a solvent-mediated change of chemoselectivity was not observed in a THF–methanol solvent mixture.

(12) Feldman, K. S.; Ensel, S. M. *J. Am. Chem. Soc.* **1994**, *116*, 3357.

(13) (a) Blomberg, C. *Bull. Soc. Chim. Fr.* **1972**, 2143. (b) Beak, P.; Yamamoto, J.; Upton, C. J. *J. Org. Chem.* **1975**, 40, 3052. (c) Wege, D. *Aust. J. Chem.* **1971**, *24*, 1531.

0022-3263/95/1960-4982$09.00/0

Scheme 1

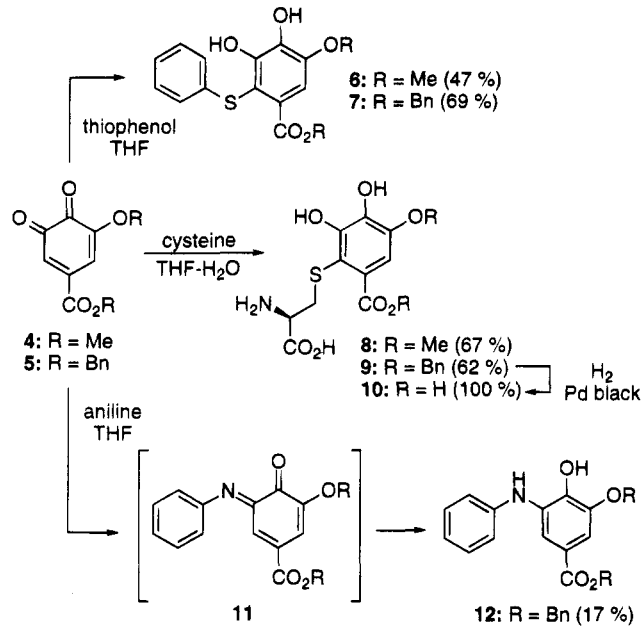
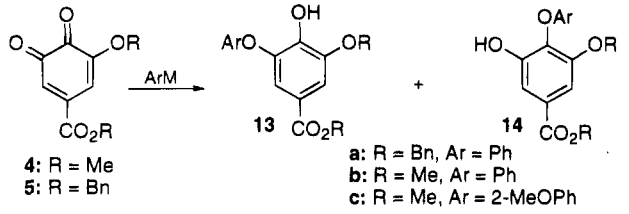


Table 1. Diaryl Ethers *via* Oxophilic Addition to Quinonoid Carbonyls



entry	quinone	ArM, conditions[a]	13:14 ratio[b]	isolated yield (%)
1	**5**	PhMgBr, RT	2:1	23
2	**5**	PhMgBr, -78°C	3:1	55
3	**4**	PhMgBr, -78°C	1.8:1	50
4	**4**	PhMgBr, CuI cat./-78°C	3:1	66
5	**4**	PhMgBr, CuI cat./-90°C	5.5:1	60
6	**4**	PhMgBr, $CeCl_3$/-90°C	5.2:1	75
7	**4**	2-MeOPhMgBr, CuI cat./-90°C	1:1	37
8	**4**	2-MeOPhMgBr, $CeCl_3$/-90°C	1:1	47

[a] Reactions were performed in THF or THF–Et_2O using 1.5–2.0 equiv of Grignard reagent; best results were obtained by adding the Grignard reagent to a solution of *o*-quinone, containing the metallic additive; see supporting information. [b] Regiochemistry was determined by methylation and $^1H/^{13}C$ NMR analyses.

dium (THF–1 M aqueous NaOH, pH apparent = 10) to ensure participation of the nonionized ϵ-amino group,[7h] gave a complex mixture; no pure adduct could be isolated.[6b,10] Aniline gave a complex product mixture upon reaction with **5**, but the monoanilino-adduct **12**[8] could be isolated as the predominant product in 17% yield. Its formation can be rationalized by citing condensation of aniline at the C-1 carbonyl carbon of **5** to give the corresponding quinone imine **11** followed by *in situ* reduction of this species with some hydroquinone moiety produced in the reaction medium (Scheme 1).[11] Thus, the preliminary evidence in hand supports a scenario wherein cystyl residues may be responsible for attachment of proteins to galloyl-derived *o*-quinones.

The reactivity of *o*-quinones **4** and **5** toward aryl-bearing organometallic reagents was next investigated, notably because of an interest in total synthesis of biaryl- and diaryl ether-containing ellagitannins.[12] Biaryl moieties would result if conjugate addition is followed, but diaryl ether units might be accessible if heterophilic addition to the quinonoid carbonyl is operational.[13] The results of these studies are summarized in Table 1. Addition of PhMgBr to *o*-quinone **5** at room temperature afforded the regioisomeric diaryl ethers **13a** and **14a** in a 2:1 ratio and 23% yield (entry 1). This modest yield was increased to 55% by simply performing the reaction at −78 °C (entry 2). Diaryl ethers **13b** and **14b** were obtained in a 3:1 ratio and 66% yield when CuI was included in the reaction medium (entries 3 and 4), and the regioselectivity was further improved at −90 °C (entry 5). It is noteworthy that utilization of cuprate reagents of the general form PhRCuM (R = Ph, Br and M = MgBr, Li) was unsuccessful, the major product being in every case the hydroquinone formed from simple reduction of **4** or **5**. The highest yield was obtained by utilizing the Grignard reagent in concert with cerium(III) chloride, a reagent known for its oxophilic character[14] (entries 6 and 8). Addition of the Grignard reagent derived from 2-bromoanisole to *o*-quinone **4** gave rise to an equimolar mixture of diaryl ethers **13c** and **14c** in only moderate yields (entries 7 and 8). Further development of this promising methodology as an alternative to the Ullmann condensation for accessing ellagitannin diaryl ethers[12] is currently in progress.

In summary, important characteristics of galloyl-derived *o*-quinone reactivity revealed by this preliminary study include (1) the efficient capture of these electrophilic species by thiol-based nucleophiles, notably the amino acid cysteine which may play a key role in the antiviral activity of gallotannins in insect herbivores, and (2) the propensity of the quinonoid carbonyls to undergo oxophilic attack by aryl-bearing organometallic reagents to furnish diaryl ethers, which may be a useful alternative to the Ullmann coupling procedure.

Acknowledgment. This work was supported by the NSF under the auspices of IBN-9407308.

Supporting Information Available: Experimental procedures and full spectral characterization for **4**–**10** and **12**–**14** (11 pages).

JO950983W

(14) (a) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.