calf spleen (CSP) phosphodiesterases (a 3′-exonuclease and a 5′-exonuclease, respectively) relative to β-dT_{28} and α-dT_{28} (Table II).[16] Particularly, CSP hydrolyzed the oligothymidylate 1 to the extent of 11% after 24 h at 37 °C. Under these conditions, α-dT_{28} was 40% hydrolyzed whereas β-dT_{28} was completely hydrolyzed within 15 min. β-dT_{28} was also completely digested by SVP within 15 min at 37 °C. However, the hydrolysis of α-dT_{28} by this phosphodiesterase was slower than the hydrolysis of β-dT_{28} but was at least 2 times faster than the hydrolysis of the oligothymidylate 2. The incubation of α,β-dT_{28} (1) with S1 nuclease (predominantly an endonuclease) for 8 h at 37 °C led to the partial hydrolysis of the oligothymidylate (12%, Table II). In contrast, β-dT_{28} and S-dT_{28} were completely hydrolyzed by S1 nuclease within 15 and 30 min, respectively, under identical conditions.

In conclusion, we have demonstrated that the α,β-oligothymidylates 1 and 2 were easily prepared and formed stable hybrids with complementary DNA and RNA sequences that had T_m values similar to those obtained with the phosphorothioate oligomer S-dT_{28}. We have also shown that 1 and 2 were resistant to endonucleolytic and exonucleolytic hydrolysis relative to β-dT_{28}, α-dT_{28}, and S-dT_{28}. To further assess the potential of alternating α,β-oligodeoxyribonucleotides with alternating (3′→3′)- and (5′→5′)-internucleotidic phosphodiester linkages as antisense molecules, the preparation of oligomers having the four different nucleobases is in progress in our laboratory. The ability of these oligonucleotide analogues to form a sequence-specific triple helix with large double-helical DNA in vitro or target particular mRNA in HIV-infected cells will be determined, and the data will be reported in due course.

Supplementary Material Available: General procedures regarding the preparation of the deoxyribonucleoside phosphoramidites and their precursors required for the solid-phase synthesis of the oligothymidylates mentioned in this paper along with a general procedure for the derivatization of long chain alkylamine controlled pore glass (LCAA-CPG) with nucleoside analogues (3 pages). Ordering information is given on any current masthead page.

(16) The conditions for the enzymatic digestion of the oligothymidylates were the following: (i) To 0.6 $O.D_{260}$ of oligothymidylate was added 60 μL of 1 M Tris·HCl (pH 9), water to a total volume of 597 μL, and 3 μL of snake venom phosphodiesterase (*Crotallus durissus*, 9 × 10^{-3} U); (ii) To 0.6 $O.D_{260}$ of oligothymidylate was added 60 μL of 1 M ammonium acetate (pH 6.5), water to a total volume of 599 μL, and calf spleen phosphodiesterase (4 × 10^{-3} U, 1 μL); (iii) To 0.3 $O.D_{260}$ of oligothymidylate was added 30 μL of 10X S1 buffer (0.33 M sodium acetate pH 4.5, 0.5 M sodium chloride, 0.3 mM zinc sulfate), water to a total volume of 298 μL, and S1 nuclease (20 U, 2 μL). These digestion reaction were incubated at 37 °C. Aliquots (100 μL) of the digests were withdrawn at various time points, added to concentrated ammonium hydroxide (500 μL), and subsequently evaporated to dryness under reduced pressure. The hydrolyzates were dissolved in water (75 μL) and directly analyzed by an Applied Biosystems Model 270A Capillary Electrophoresis instrument equipped with Micro-Gel_{100} capillaries operating at 300 V/cm in 75 mM Tris–phosphate buffer (pH 7.6) containing 10% methanol. Unless otherwise indicated (Table II), the estimated percentage of oligonucleotide hydrolysis is defined as the integrated area under the peaks corresponding to fragments smaller than the full length oligomer.

Mechanism of Conjugate Additions of Dialkylcuprates to Bromonaphthoquinones

Carl T. Wigal*

Department of Chemistry, Idaho State University, Pocatello, Idaho 83209

John R. Grunwell and James Hershberger

Department of Chemistry, Miami University, Oxford, Ohio 45056

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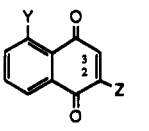
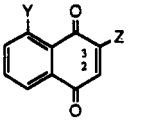
Summary: The correlation of bromonaphthoquinone redox potentials with reactivity toward dialkylcuprates reveals that the conjugate addition of Gilman reagents to bromojuglones proceeds via a single-electron-transfer mechanism.

Lithium dialkylcuprates (R_2CuLi·LiI) are known to react with α,β-unsaturated carbonyl compounds to give the corresponding β-alkylated enolate.[1] However, despite efforts since the early sixties, the detailed mechanism of this conjugate addition remains uncertain. Copper(III) is often suggested as a plausible intermediate,[2,3] but there remains the question of how the copper(III) intermediate is formed. Two accepted working hypotheses are: (1) direct nucleophilic addition of the organocopper species to the β-position and (2) stepwise addition consisting of an initial single-electron transfer (SET) from the cuprate to the carbonyl compound followed by combination of the carbonyl radical anion with the oxidized cuprate complex.[2]

In this paper we show that the regiochemistry of conjugate addition to bromonaphthoquinones 1 and 2 allows unambiguous distinction between the direct addition and SET pathways, and that the SET mechanism is in fact operative in these reactions.





1	Y = OH	Z = Br	2	Y = OH	Z = Br
3a	Y = OH	Z = t-Bu	4a	Y = OH	Z = t-Bu
3b	Y = OH	Z = Me	4b	Y = OH	Z = Me
6	Y = OAc	Z = Br	5	Y = H	Z = Br
9	Y = O-	Z = Br	7	Y = OAc	Z = Br
			8	Y = O-	Z = Br

According to FMO theory direct nucleophilic conjugate addition to bromojuglones 1 and 2 should occur at the unsubstituted carbon, which has the largest LUMO coefficient.[4,5] In fact, regiospecific nucleophilic additions

(1) (a) House, H. O.; Repress, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128. (b) Posner, G. H. *Org. React.* **1972**, *19*, 1.
(2) (a) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York, 1980. (b) Bertz, S. H.; Dabbagh, G.; Mujsce, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 631.
(3) Bertz, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1989**, *111*, 8276.
(4) Rozeboom, M. D.; Tegmo-Larson, I. T.; Houk, K. N. *J. Org. Chem.* **1981**, *46*, 2338.
(5) Grunwell, J. R.; Karipedes, A.; Wigal, C. T.; Heinzman, S. W.; Parlow, J.; Surso, J. A.; Clayton, L.; Fleitz, F. J.; Daffner, M.; Stevens, J. E. *J. Org. Chem.* **1991**, *56*, 91.

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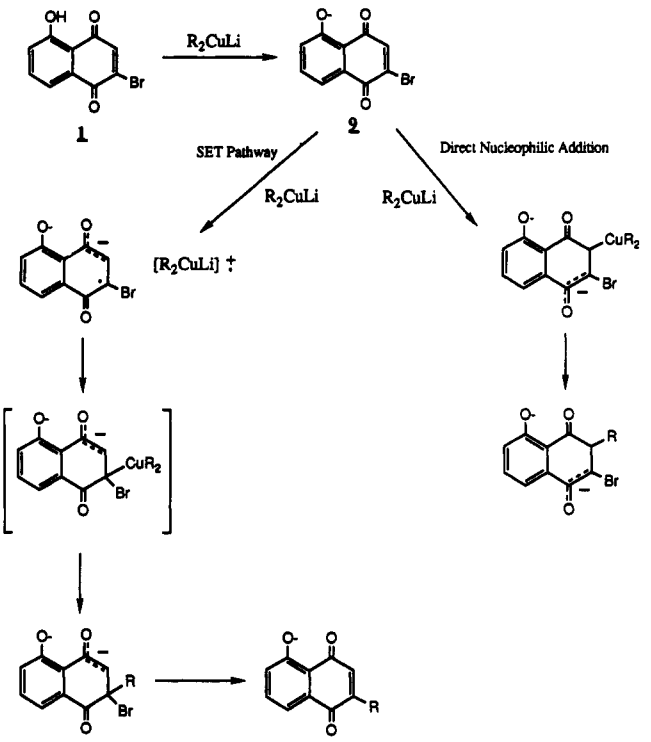
Scheme I



to the unsubstituted carbon to yield alkylated bromonaphthoquinones has been observed.[5] We have performed MNDO[6] calculations on the deprotonated bromonaphthoquinones **8** and **9**. The LUMO coefficients for **8** are 0.350 at C-3 and 0.371 at C-2, for **9** they are 0.365 at C-3 and 0.360 at C-2. Furthermore, calculations of charge at C-2 and C-3 as a function of nucleophile distance from **8** and **9** show that addition to the carbon bearing halogen is disfavored by increasing negative charge density on the carbon as the nucleophile approaches bonding distance, whereas the charge on the carbon not bearing the halogen is essentially unaffected by the approaching nucleophile.[6b] If, however, the conjugate addition proceeds with an initial SET, the radical dianions derived from the addition of a single electron to **8** and **9** are intermediates. Spin density calculations,[7] which are known to give a reliable account of the spin density distribution of radicals derived from hydroxynaphthoquinones,[8] reveal that the carbon bearing halogen has the higher spin density:[6c] for the radical dianion of **9**, the McLachlan spin densities at C-2 and C-3 are 0.454 and −0.473, respectively. For the radical dianion of **8** they are 0.192 and 3.86, respectively. Thus it is reasonable to expect coupling between the radical dianion and the oxidized cuprate complex to occur at the carbon bearing the halogen. Scheme I summarizes the two mechanistic pathways for **1**.[9] The two mechanisms predict different regiospecificity for conjugate additions to **1** and **2**. This striking dichotomy arises from the peculiar electronic attributes of the bromojuglone anions, which are the reactive species under the strongly basic conditions of cuprate additions.

Table I

compd	$E°$ (V)	product[a] (isolated % yield)
1	−0.37, −1.06	**3a** (45)
		3b (42)
2	−0.38, −1.06	**4a** (40)
		4b (39)
5	−0.47, −1.16	**5** (80–85)
6	−0.34, −0.93	**1** (87–92)
7	−0.33, −0.88	**2** (83–87)
8	−0.51, <−1.3[b]	-
9	−0.53, <−1.3[b]	-

[a] Product of the reaction with lithium dimethylcuprate or lithium di-*tert*-butylcuprate. [b] The second reduction potential wave was obscured by the reduction of Li cation.

The results of reactions of excess lithium di-*tert*-butylcuprate and lithium dimethylcuprate with **1** and **2** are summarized in Table I.[10] In each instance the sole addition product was that resulting from attack at the carbon bearing the halogen. The regiochemistry of the products is confirmed by spectral evidence, the melting point of **4b**,[11] and comparison of **3b** (the natural product Plumbagin[11]) with an authentic sample.

The reaction of cuprates with **5**, **6**, and **7** (Table I) resulted upon standard workup, in the isolation of starting material or, in the case of the acetates **6** and **7**, the simple ester hydrolysis products. No addition products were formed. Solution IR and UV–vis spectroscopy of the reaction solutions immediately following the addition of cuprate to quinone revealed that quinones **5**, **6**, and **7** had undergone a two-electron reduction to give the corresponding hydroquinone dianion.[12] In order to understand the failure of certain quinones to undergo alkylation, we measured the reduction potentials of a series of bromonaphthoquinones (Table I).[13] House and Umen[14] correlated cuprate addition with reduction potentials of a series of unsaturated carbonyl compounds. They found compounds that accept an electron at potentials less negative than −2.4 V react with R_2CuLi. Compounds that accept a second electron at potentials less negative than −1.2 V are reduced by R_2CuLi to give the dianion with no alkylation; those which accept a second electron only at potentials less than −1.2 V give the corresponding alkylated enolate. By the House criterion, only the deprotonated bromojuglones **8** and **9** are expected to give alkylation products; the bromonaphthoquinones **5**, **6**, and **7** fall within the two-electron reduction window, and thus no alkylation is observed. The successful correlation of the quinone redox potentials with their reactivity toward lithium di-

(6) (a) Calculations were performed on an IBM 4381 Model 23 employing the version of MNDO (Dewar, M. J. S.; Theil, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899) in MOPAC Version 4.0. (b) Results from calculations of hydride at a set distance from C-2 or C-3 of **8** or **9** in an optimized trajectory. Net atomic charges as a function of nucleophile distance and atomic coordinates are provided in the supplemnetary material. (c) A complete tabulation of McLachlan spin densities for the radical dianions derived from the addition of an electron to **8** and **9** is given in the supplementary material.

(7) McLachlan, A. D. *Mol. Phys.* **1960**, *3*, 233.

(8) Ahmed, I. M.; Hudson, A.; Alberti, A. *J. Organomet. Chem.* **1987**, *333*, 9.

(9) Recent studies show that unsaturated esters and ketones react with cuprates via the initial formation of a π-complex. It seems likely that a similar complexation occurs prior to σ bond formation between a cuprate and the quinoid substrates of the present study. See ref 3 and Christenson, B.; Olsson, T.; Ullenius, C. *Tetrahedron* **1989**, *45*, 523.

(10) Reactions were carried out in THF at −78 °C under nitrogen. Cuprates were prepared by standard methods from CuI and the corresponding alkyllithiums and were added to the quinones via inverse addition in a 5:1 excess.

(11) Fieser, L. F.; Dunn, J. T. *J. Am. Chem. Soc.* **1936**, *58*, 572.

(12) Standard workup consisted of acidification, aqueous extraction, and flash chromatography on silica gel. The observed products result from atmospheric oxidation of the hydroquinones.

(13) Reduction potentials were measured by cyclic voltametry using a Pt working electrode and a saturated NaCl–SCE as a quasi-reference electrode. The solvent was MeCN (or THF for substrates **8** and **9**) containing 0.2 M tetrabutylammonium perchlorate. Anions **8** and **9** were generated by in situ deprotonation of **1** and **2** with butyllithium/hexane at −78 °C. All reported potentials are relative to the ferrocene/ferrocenium couple (E' = +0.31 V).

(14) House, H. O.; Umen, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 5495.

alkylcuprates is further evidence that the conjugate addition reaction proceeds via the SET mechanism.

Supplementary Material Available: Details concerning the calculation methods, cartesian coordinates for optimized structures of 8 and 9, net atomic charges at C-2 and C-3 of 8 and 9 as a function of approaching nucleophile distance, and McLachlan spin densities for non-hydrogen atoms of the radical dianions derived from single-electron reduction of 8 and 9 (7 pages). Ordering information is given on any current masthead page.

Regiochemical Control in the Homo-Diels–Alder Reaction: Substituent Effects

Mark Lautens*,[1a] and Louise G. Edwards[1b]

Department of Chemistry, University of Toronto, Toronto, Ontario Canada M5S 1A1

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Summary: The regio- and stereoselectivity of the cycloaddition between substituted norbornadienes and electron-deficient olefins catalyzed by nickel complexes has been studied. The diene and dienophile substituents as well as the ligand were found to exert a dramatic effect on the selectivity.

We have recently reported improvements in the facility and stereoselectivity of the [2 + 2 + 2] homo-Diels–Alder reaction (HDA) between norbornadiene and activated olefins in the presence of nickel catalysts.[2a] This reaction has tremendous potential for use in the construction of complex polycycles since two new rings, as well as up to seven new stereocenters, are created in a single operation, eq 1.

(1)

Unlike the Diels–Alder reaction (where predictable and high regioselectivity is expected in a cycloaddition between an electron-rich diene and an electron-poor dienophile),[3] little is known about the regiochemical outcome of an analogous HDA reaction as there exists only one example of a successful cycloaddition between a substituted norbornadiene and a dienophile, eq 2.[4] In this instance,

(2)

TCNE, a symmetrical and highly reactive dienophile, approaches from the unsubstituted side of diene 2 to give the substituted cyclopropane derivative 3. Other attempts to promote the cycloaddition with substituted norbornadienes or other types of homoconjugated dienes have been unsuccessful.[4,5] With the advent of highly reactive catalysts,[2a,b] we chose to examine the cycloaddition between norbornadienes bearing an electron-donating or -withdrawing group and electron-deficient olefins. From the outset of this study, we were aware that as many as eight isomers *could* be formed when both the diene and dienophile are unsymmetrical; thus, high levels of regioselectivity would be necessary before the reaction could become synthetically useful. The structures of the isomers, designated ortho, meta, meta', and para, are shown in Scheme I. Exo and endo isomers are possible for each cycloadduct. This paper describes our preliminary studies in this area, which indicate that selective cycloadditions are possible.

Scheme I

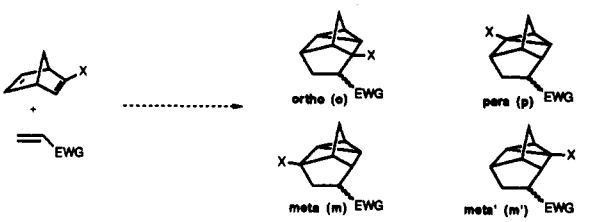

Table I. Cycloaddition of Methyl Norbornadiene-2-carboxylate (4) Using $Ni(COD)_2/2PPh_3$

			ratio of isomers (exo:endo)			
entry	dienophile	% yield	para	meta'	meta	ortho
1	acrylonitrile[a]	94	1 (1:2.3)[b]	0	0	0
2	acrylonitrile[a,c]	65	1 (1:1)	0	0	0
3	phenyl vinyl sulfone[a]	75[d]	2 (1:0)[e,f]	1 (1:0)[f]	0	0
4	methyl vinyl ketone[a]	88[g]	7 (2.8:1)	1 (1:1)	0	2 (0:1)
5	methyl vinyl ketone[a,h]	48	3.8 (1:3.2)	1 (0:1)	0	6.9 (0:1)

[a] At 80 °C in 1,2-dichloroethane. [b] The endo/exo ratio increased with increasing temperature. [c] Catalyst was $(Ph_3P)_2Ni(CO)_2$. [d] At room temperature, the yield decreased to 9%. [e] The ratio appeared to be unaffected by reaction temperature. [f] The regiochemistry assigned to the major and minor isomers may be reversed, see text. [g] At room temperature, the yield decreased to 25%. [h] Catalyst was $Ni(COD)_2/2P(O^iPr)_3$.

In order to study the effect of substitution on the diene, substrates 4 and 5 were prepared[6] and reacted with several

(1) (a) Fellow of the Alfred P. Sloan Foundation, 1991–1993. NSERC(Canada) University Research Fellow 1987–1992. BioMega Young Investigator 1990–93. (b) NSERC(Canada) Postgraduate Scholar 1987–1991.

(2) (a) Lautens, M.; Edwards, L. G. *Tetrahedron Lett.* **1989**, *30*, 6813 and references cited therein. (b) For cycloadditions catalyzed by cobalt, see: Lautens, M.; Crudden, C. M. *Organometallics* **1989**, *8*, 2733. Lautens, M.; Lautens, J. C.; Smith, A. C. *J. Am. Chem. Soc.* **1990**, *112*, 5627. Lyons, J. E.; Myers, H. K.; Schneider, A. Transition Metal Mediated Organic Synthesis. *Ann. N.Y. Acad. Sci.* **1980**, *333*, 273. Brunner, H.; Muschiol, M.; Prester, F. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 652.

(3) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley Interscience, New York, 1985.

(4) Fickes, G. N.; Metz, T. E. *J. Org. Chem.* **1978**, *43*, 4057.

(5) Kelly, T. R. *Tetrahedron Lett.* **1973**, *14*, 437.

(6) (a) Methyl norbornadiene-2-carboxylate was prepared by adsorbing a mixture of methyl propiolate (791.5 mg, 9.4 mmol) and freshly cracked cyclopentadiene (1.60 g, 19.4 mmol) onto activated silica gel (22.5 g). This mixture was allowed to stand for 7–9 days, and the product was eluted with ether. After removal of the solvent in vacuo, the product was purified by flash chromatography on silica gel or vacuum distillation (bp 78 °C (5 mmHg), 1.16 g, 82%). Yields ranged from 78–97%. This method was developed since existing methods proved to be capricious in our hands, see: Graham, P. J.; Buhle, E. L.; Pappas, N. *J. Org. Chem.* **1961**, *26*, 4658. Corey, E. J.; Shibasaki, M.; Nicolaou, K. C.; Malmsten, C. L.; Samuelsson, B. *Tetrahedron Lett.* **1976**, *17*, 737. For the use of silica gel to promote cycloadditions, see: Veselovsky, V. V.; Gybin, A. S.; Lozanova, A. V.; Moiseenkov, A. M.; Smit, W. A.; Caple, R. *Tetrahedron Lett.* **1988**, *29*, 175. (b) 2-Methoxynorbornadiene was prepared as described by Jefford, see: Jefford, C. W.; Huy, P. T. *Tetrahedron Lett.* **1980**, *21*, 755. Barbot, F.; Miginiac, P. *Helv. Chim. Acta* **1979**, *62*, 1451.

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