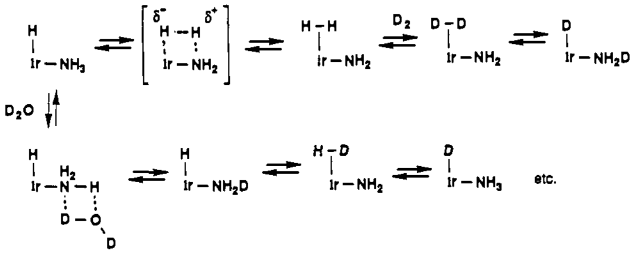
Scheme III



process may be viewed as an intramolecular version of the deprotonation of a dihydrogen ligand.[11,12] A similar equilibrium involving an η^2-H_2 intermediate was proposed for $Ir(H)(H_2O)(bq)(PPh_3)_2^+$ (bq = benzoquinolinate) although the H_2O ligand is easily displaced upon treatment with H_2[5] as opposed to the tightly bound NH_3 in **1–5**. Also relevant is the reaction of complexes of the ligand $N(SiMe_2CH_2PPh_2)_2$ with H_2 to yield the corresponding amine metal hydrides.[13] Dihydrogen complexes containing nitrogen donor ligands have been reported.[14]

The degree to which the ammine ligands undergo H/D exchange reflects (a) the requirement for the NH_3 and hydride ligands to be mutually cis and (b) the higher acidity of the NH_3 trans to the π-accepting cyclooctene ligand.

Parallel to the NH_3/Ir-H exchange process, an olefin-hydride/alkyl equilibrium in complexes **1** and **2** results in label transfer from the ammine ligand to the olefin (Scheme II). The lack of scrambling between the three types of ammine ligands suggests a square-pyramidal structure for the alkyl intermediate. Obviously, the olefin-hydride arrangement prevails over that of the alkyl, which could not be detected spectroscopically. This may be a result of the importance of π-back-bonding to the olefin, the only π-acceptor present in these electron-rich complexes. The fairly slow exchange rate has precluded attempts to quantify it by spin saturation transfer experiments.

The phosphine complexes **3–5** also show interesting exchange reactivity. Although they are classical hydrides on the basis of T_1 measurements, exposure to D_2 leads to deuterium incorporation into both Ir-H and N-H bonds. When THF solutions of the complexes are placed under 30 psi of D_2 for 7 days at room temperature, **3–5** incorporate 4.7, 20, and 47% deuterium, respectively, the ratio of N-D/Ir-D being 1.4:1. The order of exchange reactivity **3** < **4** < **5** parallels the trend of increasing electron density on the metal center. The monocationic complex **5** experiences higher electron density than the dicationic **4**, which, in turn, is more electron rich than the phosphine complex **3**.

Since amines do not undergo exchange with D_2 in the absence of a catalyst,[15,16] intermediacy of a nonclassical dihydrogen complex is implied (Scheme III). Generation of such an intermediate may be favored with increasing electron density at the metal, as a result of a more "basic" hydride, facilitating the intramolecular "deprotonation" of bound NH_3. Intermediacy of an η^2-H_2 complex was suggested for the D_2O/H_2 exchange catalyzed by $Ru(OEP)(THF)_2$ in the presence of KOD.[12]

An alternative mechanism of Ir-H/N-H exchange involving generation of an ammonium salt by deprotonation of the hydride ligand with a dissociated ammonia molecule is highly unlikely. Such a mechanism is not compatible with preferential D incorporation in the *cis*-NH_3 groups of **1** and **2**. Moreover, exposure of complex **1** to $^{15}NH_3$ did not lead to ^{15}N incorporation.

As expected, complexes **1–5** also undergo exchange with D_2O. N-H/O-D scrambling is the fastest process occurring after minutes at room temperature and is followed by slow generation of Ir-D and (in complexes **1** and **2**) C-D bonds occurring to a noticeable extent after a few hours. In principle, complete deuteration of the bound cyclooctene ligand can be achieved in this way, representing several cycles of C-H/O-D exchange. Similar exchange occurs between **1–5** and ND_3.

The equilibrium processes described here open up a new means of labeling coordinated olefins by, e.g., D_2O, ND_3, or D_2. We are now exploring the possibility of a catalytic process under conditions which allow equilibrium between free and coordinated olefins. Utilization of complexes such as **5** as catalysts for labeling water and ammonia may also be possible.

Acknowledgment. This research was supported by Grant No. 89-00374 from the U.S.-Israel Binational Science Foundation (BSF), Jerusalem, Israel, and by the Fund for Basic Research, administered by the Israel Academy of Sciences and Humanities. We thank Prof. R. Bau of the University of Southern California for useful discussions.

Registry No. 1, 136457-90-4; **2**, 136457-91-5; **3**, 136358-03-7; **4**, 136358-05-9; **5**, 136358-07-1.

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Origin of the Regioselectivity in the Photochemical Cycloaddition Reactions of Cyclic Enones with Alkenes: Chemical Trapping Evidence for the Structures, Mechanism of Formation, and Fates of 1,4-Biradical Intermediates[1]

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The cycloaddition of alkenes to the triplet excited state of cyclic enones is known to involve the intermediacy of triplet 1,4-biradical species which proceed to cyclobutane products in competition with reversion to the ground-state precursors (Scheme I).[2] For alkenes substituted by a polar group, the reaction exhibits some regioselectivity. Electron-rich alkenes such as ethyl vinyl ether yield the "head-to-tail" isomer **1** in preference to the "head-to-head" isomer **2**, whereas electron-poor alkenes such as acrylonitrile selectively yield the analogous head-to-head structure.[2,3] However, recent work has indicated that some electron-poor alkenes, such as α,β-unsaturated esters, do not always follow this rule.[4]

The regioselectivity is commonly explained in terms of the formation of a complex between the triplet excited state of the enone and the alkene in which the excited-state dipole is aligned with that of the ground-state alkene so as to maximize electrostatic attraction.[2] This oriented exciplex presumably would lead to preferential formation of those biradicals which generate the appropriate regioisomer. An alternative explanation has been suggested,[2d,5] namely, that the regiochemistry is determined by

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[1] Contribution number 442 from the Photochemistry Unit, University of Western Ontario.

[2] (a) de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41. (b) Loutfy, R. O.; de Mayo, P. *J. Am. Chem. Soc.* **1977**, *99*, 3559. (c) Weedon, A. C. In *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum Press: New York, 1984; pp 61–144. (d) Schuster, D. I. In *The Chemistry of Enones*; Patai, S., Rappoport, Z., Eds.; Wiley: Chichester, 1989; pp 623–756.

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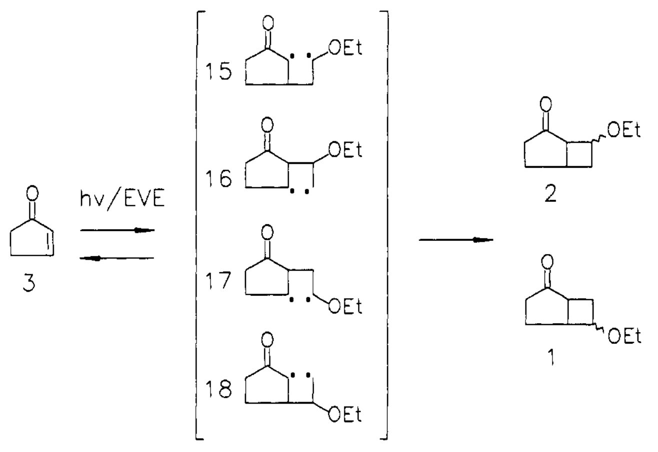
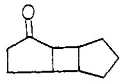
Scheme I



the relative efficiencies with which each of the isomeric biradical intermediates shown in Scheme I proceeds to the cyclobutane product rather than reverting to the ground-state precursors. In order to distinguish between these two possibilities, either the biradical intermediates must be prepared by an independent route and their fates monitored or they must be intercepted by a chemical trap so that their structures and relative rates of formation can be inferred. We report here on the first results of an examination of the latter approach.

The chemical trap used for the study was hydrogen selenide. This was chosen because the lifetime of the triplet 1,4-biradicals is too short for them to be intercepted by more common radical traps[6] and because Kambe et al. have reported[7] that hydrogen selenide is effective as a hydrogen atom donor for the interception of the 1,4-biradical intermediates generated in the Norrish type II reaction of ketones. The viability of this reagent for the interception of 1,4-biradicals generated in enone photocycloaddition reactions was tested using the reaction of 2-cyclopentenone (**3**) with cyclopentene.



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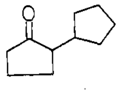

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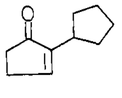

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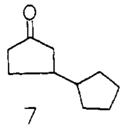

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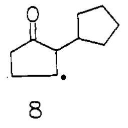

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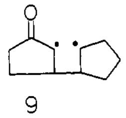

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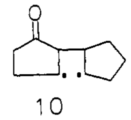

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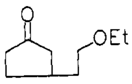

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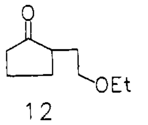

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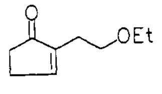

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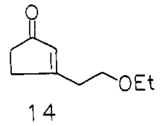

14

Ultraviolet light irradiation of a benzene solution of **3** (0.06 M) containing cyclopentene (1.2 M) gave the previously described adduct **4** as a mixture of cis-syn-cis and cis-anti-cis stereoisomers. Repetition of the reaction under identical conditions except that the solution also contained H_2Se (0.3 M) gave a mixture of products, none of which were the cycloadducts. Analysis of a sample of the reaction mixture which had not been exposed to the UV source indicated that some of these products resulted from thermal reaction between the hydrogen selenide and **3** and the cyclopentene.[8] Three products were formed in the photochemical reaction which were not present in the dark reaction. These were assigned structures **5–7**. Compounds **5** and **7** are presumed to arise from reduction of the biradical intermediates by H_2Se, while **6** is presumed to be formed by disproportionation of the intermediate radical **8** with hydrogen selenyl radical. The ratio of products **5–7** in the reaction mixture was 3.0:6.0:8.2, respectively.[9]

The absence of cycloadducts among the products of irradiation in the presence of H_2Se confirms that all of the intermediate biradicals were trapped. The ratio of **5** + **6** to **7** formed is 9.0:8.2 and suggests that mixtures of stereoisomers of the regioisomeric biradicals **9** and **10** are formed in similar amounts. The site of initial bonding in the photocycloaddition reactions between enones and alkenes has long been a subject of controversy.[2,10] We have recently shown that in the reaction between **3** and vinylcyclopropane initial bonding occurs at both the α and β positions of the enone;[6] the formation of **5–7** described here suggests that this is also true for the reaction between 2-cyclopentenone and cyclopentene.

Repetition of the reaction with ethyl vinyl ether (EVE) as the alkene gave, in the absence of H_2Se, compounds identified as the structural isomers **1** and **2** in the ratio 3.1:1.0. Each was formed as a mixture of stereoisomers, as has been reported previously.[11] When H_2Se was present, compounds identified as **11–14** were isolated as the only photochemical products in the ratio 5.7:3.2:3.5:1.0, respectively. None of the cycloadducts **1** and **2** were observed. The cyclopentenone-containing products are presumed to arise from disproportionation of the partially trapped biradicals with hydrogen selenyl radical. The structures of the trapped products suggest that in the reaction of **3** with EVE only the biradicals **15** and **17** are formed as intermediates and none of the alternative, less stable biradicals **16** and **18**. This implies a previously unproven conclusion, namely, that in enone photocycloaddition reactions the excited enone initially becomes attached to the less substituted end of the alkene. The relative yields of the trapped products indicate that the biradicals **15** and **17** are formed in the ratio 1.0:1.0. This must mean that the rates of formation of these biradicals are the same and suggests that the rate constants for formation of the biradicals from interaction of the alkene with the triplet excited enone are also the same if an exciplex intermediate is not involved in the reaction. Comparison of the ratio of the head-to-head to the head-to-tail cycloadducts **2** and **1** obtained in the absence of hydrogen selenide with the ratio of regioisomeric biradicals **15** and **17** trapped by H_2Se suggests

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(5) (a) Bauslaugh, P. G. *Synthesis* **1970**, 287. (b) Schuster, D. I.; Heibel, G. E.; Brown, P. B.; Turro, N. J.; Kumar, C. V. *J. Am. Chem. Soc.* **1988**, *110*, 8261.

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(8) The structures of the dark reaction products suggest that, in addition to being a good hydrogen atom donor, H_2Se is apparently a strong enough acid (pK = 3.9) to catalyze slow electrophilic addition to reactive alkenes and a sufficiently powerful nucleophile to attack enones in a Michael sense.

(9) A referee has suggested that the trapped products could arise from hydrogen abstraction by the triplet enone from H_2Se. This would produce a radical which could add to alkene; the new radical thus formed would yield the observed products if it then were to abstract a hydrogen atom from H_2Se. This possibility can be discounted since under the reaction conditions the rate of addition of a radical to an alkene would be much slower than the rate of hydrogen abstraction by the radical from H_2Se.

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that in the absence of H_2Se the regioselectivity of cycloadduct formation must have its origins in the relative efficiencies with which the two biradicals proceed to the cyclobutane adducts in competition with reversion to the ground-state enone and that the biradical **15** proceeds to products 3 times less efficiently than biradical **17**.

Our results imply that, at least for the reaction of **3** with EVE, the regiochemistry of enone cycloaddition is not governed by the orientation of the reactants in an exciplex precursor as has long been assumed. We are currently attempting to extend these results to other polar alkenes and other enones.

(*S*)-α-Amino-2,2′-bipyridine-6-propanoic Acid: A Versatile Amino Acid for de Novo Metalloprotein Design

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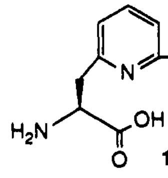
Received May 7, 1991

The de novo synthesis of metalloproteins[1] is limited by the number and diversity of *naturally* occurring metal-binding amino acids, particularly when compared to the wide variety of synthetic ligands which are available for selective complexation of metal ions in aqueous media.[2] Thus, a current objective is to expand the repertoire of protein building blocks through the design and construction of *synthetic* metal-binding amino acids that, when incorporated into a three-dimensional structural framework created by a polypeptide, may exhibit enhanced metal cation selectivities and a wider range of metal coordination geometries over those which are presently available.[3] Toward this goal, we report a preliminary evaluation of metal cation coordination to peptides which incorporate the unnatural amino acid (*S*)-α-amino-2,2′-bipyridine-6-propanoic acid (**1**), Bpa.[4]



1 (Bpa)

Ac-Bpa-Thr-Pro-D-Ala-Val-Xaa·NH$_2$

2: Xaa=Bpa
3: Xaa=Phe

The sequence of peptides studied was designed to include a central prolyl-D-amino acid dipeptide which has been shown to favor reverse turn (β-type II) formation in solution.[5] Hence, it was anticipated that the intramolecular metal-binding capabilities of **2** should be enhanced due to the proximity of the two bipyridyl side chains. In order to investigate the relative contributions of intra- and intermolecular coordination to metal binding, peptide **3** was also prepared.

Table I. Summary of Dissociation Constants for Peptides **2** and **3** with Divalent Metal Cations

metal ion	K_d,[a] M	
	2	**3**
Zn(II)	$9.6 \pm 0.6 \times 10^{-4}$[b]	$2.7 \pm 0.3 \times 10^{-3}$
Co(II)	$1.1 \pm 0.2 \times 10^{-4}$[b]	$1.1 \pm 0.1 \times 10^{-3}$
Cd(II)	$1.1 \pm 0.2 \times 10^{-4}$[b]	$4.3 \pm 0.3 \times 10^{-3}$
Ni(II)	$1.1 \pm 0.2 \times 10^{-6}$	$5.0 \pm 0.5 \times 10^{-5}$
Cu(II)	$<1.0 \times 10^{-8}$[c]	$0.8 \pm 0.2 \times 10^{-7}$

[a] Equilibrium binding constants were determined by UV spectroscopy at various metal cation concentrations at 25 °C in the presence of 200 mM NaCl. Dilute peptide solutions (<2 μM) were run in a 10-cm-path quartz cuvette; in all other cases a standard 1-cm-path cuvette was used. A minimum of three determinations were recorded in each case. [b] The peptide to metal stoichiometry was assumed to be 1:1. [c] Limiting value for K_d of **2** with Cu(II). The sensitivity of the UV method limits assessment at lower concentrations.

In the absence of metal ions, the electronic spectra of aqueous solutions of the peptides, **2** and **3**, show an absorption at 285 nm due to the bipyridyl moiety. Upon addition of divalent metal cations, this absorption decreases in intensity with the concomitant appearance of two new absorptions at around 240 and 310 nm.[6,7] Given that two well-defined isosbestic points are associated with this transformation, UV spectroscopy provides a convenient method for obtaining the dissociation constants,[8] as well as information concerning the stoichiometry of the metal-bound complexes.

As can be seen from Table I, the dissociation constants vary over 5 orders of magnitude, with the tightest binding being observed for Cu(II) and the weakest for Zn(II). The relative affinity for metal follows that predicted by the Irving–Williams order of stabilities; however, the magnitude is smaller than observed for parent complexes of 1,10-phenanthrolines and 2,2′-bipyridyl.[9] This diminished affinity is in part due to steric hindrance imposed by substitution at the 6-position of the 2,2′-bipyridyl unit of **1**.[10,11] The selectivity shown in Table I complements that reported for peptides containing unnatural oxygen-containing bidentate ligands[3b] or "zinc finger" proteins.[1c,12]

For binding of Cu(II) and Ni(II), the stoichiometry of binding was found to be 2:1 bipyridyl:metal for **2** and 1:1 for **3**. This corresponds, in each case, to a 1:1 metal ion/peptide complex. Comparison of circular dichroism titration studies of **2** and **3** with Cu(II) also provides valuable structural information and demonstrates that the metal-bound complexes are quite distinct (Figure 1). With peptide **2**, an intense, positive ellipticity at 315 nm (attributed to the bipyridyl chromophore) is observed; in contrast, a weak and broad ellipticity (310–330 nm) is seen with peptide **3**. These spectroscopic studies indicate that Cu(II) induces the

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(10) For comparison, the values for K_d for 2,2′-bipyridyl (bipy), 1,10-phenanthroline (phen), and 2-methyl-1,10-phenthroline (2-Mephen) with divalent metals M(II) are provided (see ref 9a for more examples). $K_d = [M(II)][L]/[M(II)L]$: bipy and Zn(II), $K_d = 7.4 \times 10^{-6}$ M; bipy and Ni(II), $K_d = 9.1 \times 10^{-8}$ M; bipy and Cu(II), $K_d = 4.7 \times 10^{-7}$ M; phen and Zn(II), $K_d = 4.0 \times 10^{-7}$ M; phen and Ni(II), $K_d = 2.0 \times 10^{-9}$ M; phen and Cu(II), $K_d = 3.8 \times 10^{-8}$ M; 2-Mephen and Zn(II), $K_d = 1.0 \times 10^{-5}$ M; 2-Mephen and Ni(II), $K_d = 1.1 \times 10^{-6}$ M; 2-Mephen and Cu(II), $K_d = 3.9 \times 10^{-8}$ M.

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0002-7863/91/1513-8527$02.50/0