# Photoinitiated Electron-Transfer Reactions of Aromatic Imides with Phenylcyclopropanes. Formation of Radical Ion Pair Cycloadducts. Mechanism of the Reaction

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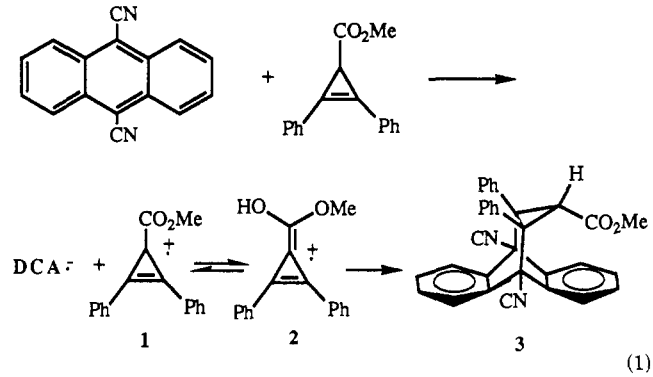
Few investigations have addressed the cyclization of a radical anion–radical cation pair resulting from photoinitiated electron transfer. One system that meets the criteria necessary to observe this phenomenon is the acceptor–donor pair *N*-methylphthalimide (NMP) and phenylcyclopropane (PC). Irradiation of NMP or *N*-methyl-2,3-naphthalimide (NMN) in the presence of PC in acetonitrile gave rise to two spiro tetrahydrofuranyl lactams. The regiochemistry and relative stereochemistry of these compounds were determined by NMR techniques and X-ray crystallography. The mechanism of the reaction proceeds via electron transfer from PC to the imide followed by coupling of the radical ion pair at the 1,2-position of the carbonyl to the cyclopropane ring in a stepwise fashion. Fluorescence quenching experiments, reaction efficiency, and the free energy for electron transfer using various aromatic substituted phenylcyclopropanes provided strong evidence that electron transfer occurs. The reaction of *cis*-2-deutero-1-phenylcyclopropane (PC-d) with NMN established that cycloaddition is stepwise rather than concerted and that both syn and anti reactive intermediates are equally accessible.

## Introduction

The nature of radical ion pairs from photochemical electron transfer reactions has been the focus of numerous studies over the past several decades.[1] One reaction that has drawn our attention most recently is the cyclization of the radical anion–radical cation pair which can proceed via a concerted process (path b, Scheme I) or a stepwise process where either radical (path a) or ionic (path c) coupling occurs first. Although this type of radical ion interaction appears to be favorable, it is usually dominated by proton transfer and reverse electron transfer reaction. Farid and Mattes have noted that the addition products of electron acceptors and electron donors are usually not the result of direct coupling of the radical ions, rather, that most are formed by proton transfer from the donor radical cation to the acceptor radical anion and then coupling of the donor radical to the acceptor radical or radical anion.[1,2]

Perhaps the closest example of radical ion pair coupling at the time of this research was reported by Farid, Mattes, and Brown-Wensley.[3] Subsequent to electron transfer from methyl 1,2-diphenylcyclopropene-3-carboxylate to excited 9,10-dicyanoanthrene (DCA), the radical cation **1** undergoes enolization to **2** followed by coupling with $DCA^{\bullet-}$ and ketonization to give **3**. Farid and co-workers did not consider this an example of radical anion–radical cation coupling because enolization of **1** occurs prior to cycloaddition.

We set out to design a system where cyclization of radical ion pairs can occur and considered the following criteria. (1) The donor cation must not deprotonate readily leading to an allyl radical. (2) The radical anion of the acceptor must be nucleophilic. (3) The donor radical cation must be susceptible to nucleophilic attack. (4) Back electron transfer must not be a dominant process ($\Phi > 0.99$). A system that meets the criteria is *N*-methylphthalimide (NMP) and phenylcyclopropane (PC). NMP has been shown to undergo photostimulated electron transfer from suitable donors,[4] and its radical anion is




(1)

readily protonated in protic solvents, suggesting that it is basic and possibly nucleophilic. Phenylcyclopropane also undergoes electron transfer to suitable acceptors[5] and, unlike many electron-rich alkenes which commonly serve as electron donors, it has no acidic protons. Nucleophilic attack on the PC radical cation has been shown to be quite efficient with alcohols,[5a,b] cyanide, and water.[5b] Hixson and Rao[5a] also suggest that, although the bond to be broken in the cyclopropyl ring of the PC radical cation remains intact, it is significantly weakened and is susceptible to nucleophilic attack. This proposition was corroborated by CINDP studies conducted by Roth and Manion-Schilling on 1,2-diphenylcyclopropane.[6]

The free energy of electron transfer from PC to NMP as determined from Weller's equation (eq 2) is exothermic

$$\Delta G = 23.06(E_{ox} - E_{red}) - E_{0,0} - e_0^2/\epsilon_a \qquad (2)$$

($\Delta G = -7.5$ kcal/mol), where $E_{ox}$ and $E_{red}$ are the oxidation potential of PC (1.83 V) and the reduction potential of NMP (−1.37 V),[7] respectively, $E_{o,o}$ the excitation energy of NMP (80 kcal/mol),[8] and $e_o^2/\epsilon_a$ is the Coulombic in-

(1) Mattes, S. L.; Farid, S. *Acc. Chem. Res.* **1982**, *15*, 80.
(2) For examples, see: (a) Lewis, F. D. *Acc. Chem. Res.* **1979**, *12*, 152. (b) Lewis, F. D.; Ho, T.-I. *J. Am. Chem. Soc.* **1977**, *99*, 7991. (c) Maroulis, A. I.; Arnold, D. R. *J. Chem. Soc., Chem. Commun.* **1979**, 351. (d) Arnold, D. R.; Wong, P. C.; Maroulis, A. J.; Cameron, T. S. *Pure Appl. Chem.* **1980**, *52*, 2609. (e) Mazzocchi, P. H.; Klingler, L. *J. Am. Chem. Soc.* **1984**, *106*, 7567.
(3) Farid, S.; Brown, K. A. *J. Chem. Soc., Chem. Commun.* **1976**, 564. Brown-Wensley, K. A.; Mattes, S. L.; Farid, S. *J. Am. Chem. Soc.* **1978**, *100*, 4162.
(4) Mazzocchi, P. H.; Minamikawa, S., Wilson, P. *Tetrahedron Lett.* **1978**, 4361. Mazzocchi, P. H.; Minamikawa, S.; Wilson, P. *J. Org. Chem.* **1985**, *50*, 2681.
(5) (a) Rao, V. R.; Hixson, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 6548. (b) Mizuno, K.; Ogawa, J.; Otsuji, Y. *Chem. Lett.* **1981**, 741. Mizuno, K.; Ogawa, J.; Lagano, H.; Otsuji, Y. *Chem. Lett.* **1981**, 437. (c) Wong, P. C.; Arnold, D. R. *Tetrahedron Lett.* **1979**, 2101.
(6) Rehm, D.; Weller, A. *Isr. J. Chem.* **1979**, *2*, 259.
(7) Leedy, D. W.; Muck, D. L. *J. Am. Chem. Soc.* **1971**, *93*, 4264.
(8) Coyle, J. D.; Newport, G. L.; Harriman, A. *J. Chem. Soc., Perkin Trans. 1* **1978**, 133.
(9) Johnson, C. K. ORTEP, Report ORNL-3794; Oak Ridge National Laboratory, Oak Ridge, TN, 1965.
(10) Jingchu, L.; Ammon, H. L.; Gilliland, G. *J. Appl. Crystallogr.* **1989**, *22*, 186.

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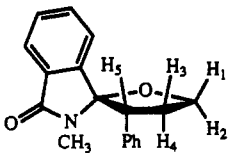
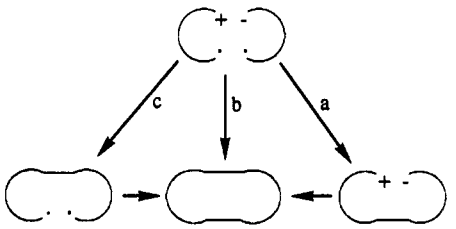


**Figure 1.** Drawing of **6** showing proton numbering in the tetrahydrofuranyl ring.

**Scheme I**

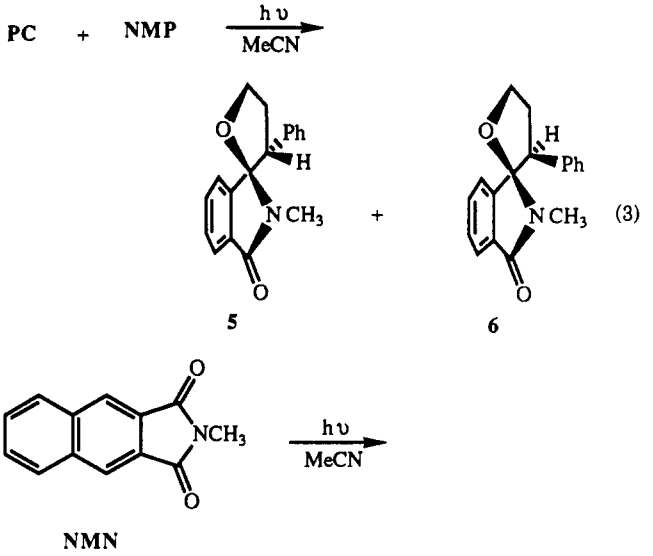


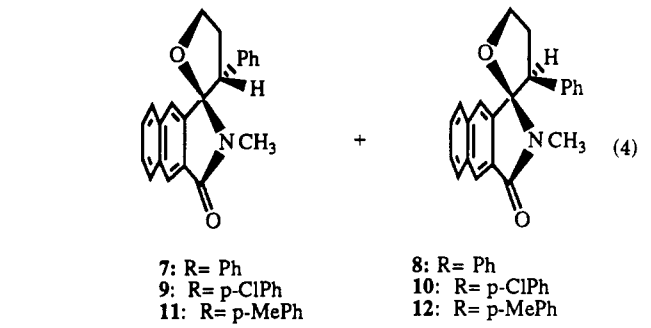
teraction between ions (1.3 kcal/mol).[6]

## Results

NMP was irradiated in the presence of PC in methanol to determine if electron transfer takes place between NMP and PC. The expected 1-methoxy-3-phenylpropane was detected (GLC) and a new product (**4**) isolated. Spectral analysis of **4** showed a hydroxyl and an amide carbonyl band in the IR spectrum and, in the $^1$H NMR spectrum, singlets at $\delta$ 4.30, 3.26, and 2.68 corresponding to the hydroxyl, methoxy, and *N*-methyl protons, respectively, a doublet of doublets at $\delta$ 4.43 for the benzylic proton, and four multiplets representing the four remaining alkyl protons. Presumably, electron transfer from PC to excited NMP is followed by nucleophilic attack by methanol on the radical cation. Coupling of the ether radical with NMP$^{\bullet-}$ and protonation affords **4**. Alternatively, back electron transfer from NMP$^{\bullet-}$ can occur followed by protonation to give 1-methoxy-3-phenylpropane (Scheme II).

In nonnucleophilic solvents, irradiation of NMP with PC afforded the spiro tetrahydrofuranyl lactams **5** and **6** in 21% combined yield (eq 3), adducts that were not found when the reaction was carried out in methanol. Similarly, irradiation of *N*-methyl-2,3-naphthalimide (NMN) with PC in acetonitrile gave the corresponding adducts **7** and **8** in a 57% combined yield (eq 4). The $^1$H NMR spectra of **5** and **6** were similar to the spectra of **7** and **8** except for the aromatic region.





**NMN**

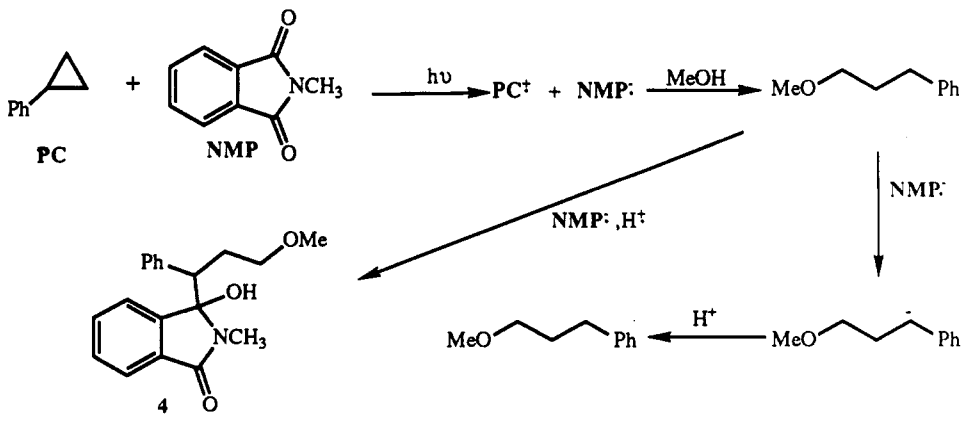


**7**: R= Ph
**9**: R= p-ClPh
**11**: R= p-MePh

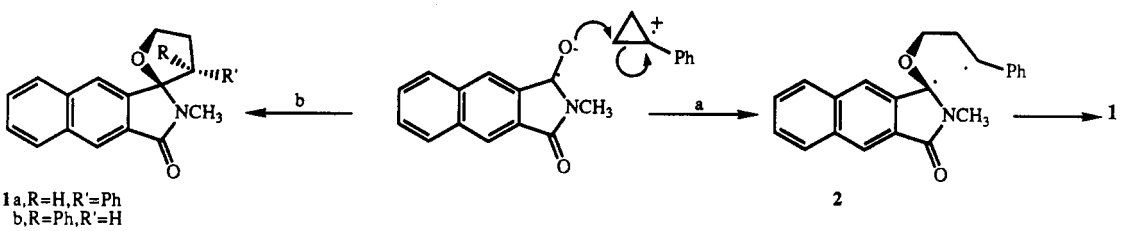
**8**: R= Ph
**10**: R= p-ClPh
**12**: R= p-MePh

The NMR spectrum of **5** showed single proton multiplets at $\delta$ 2.55, 2.85, 4.08, 4.30, and 4.58 with a three-proton methyl singlet at $\delta$ 2.78. Compound **6** had similar chemical shifts and couplings, indicating that it was isomeric except that its *N*-methyl signal was shifted downfield to $\delta$ 3.20, a downfield shift that was useful in establishing stereochemistry (vide infra). The structure of **5** was established by a series of 2-D NMR experiments. A COSY spectrum of **5** showed that the protons at $\delta$ 2.55 and 2.85 were coupled to each other and the other three aliphatic protons, whereas the protons at $\delta$ 4.30 and 4.58 were only coupled to those at 2.55 and 2.85. The proton appearing at $\delta$ 4.08 was only coupled to those resonanting at 2.55 and 2.85. These data are consistent with the structure **5** and assignments of protons H-3 and H-4 (Figure 1) to resonances at $\delta$ 2.55 and 2.85, H-1 and H-2 to resonances at $\delta$ 4.30 and 4.58, and H-5 to the one at $\delta$ 4.08. A heteronuclear shift correlation experiment indicated that the protons at $\delta$ 4.30

**Scheme II**



Scheme III



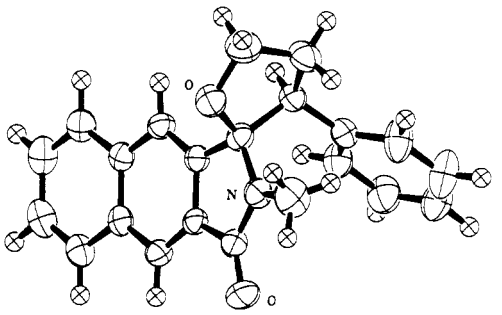




**Figure 2.** ORTEP[9] drawing of 8. The C, N, and O atoms are represented by 50% probability ellipsoids and the H atoms by $B$ = 1.5 Å spheres. The drawing was prepared on a Hewlett-Packard Laser-Jett II printer with the PLOTMD[10] program.

and 4.48 were coupled to a carbon resonating at 69.0 ppm, whereas those $\delta$ 2.55 and 2.85 were coupled to a carbon resonating at 30.0 ppm, confirming that these proton pairs were geminally coupled methylene protons.

Finally, the stereochemistry of 8 was determined by X-ray crystallography (Figure 2) to be syn; that is, the phenyl is syn to the *N*-methyl. The $^1$H NMR signal of the *N*-methyl in 8 appears at $\delta$ 2.81 and is shifted upfield due to the anisotropic effects of the phenyl substituent in comparison to the anti isomer where the signal is observed at $\delta$ 3.29; this chemical shift difference was used to determine the relative stereochemistry of all the spiro tetrahydrofuranyl lactams observed in this study.

We propose that the formation of these adducts proceeds via excitation of the imide, electron transfer to give a radical ion pair, and nucleophilic attack on the cyclopropane by the negatively charged oxygen of the imide in either a stepwise (a) or a concerted (b) process to give the observed product (Scheme III). We continued our investigations using NMN since it, unlike NMP, fluoresces providing an additional mechanistic probe. NMN has an additional advantage in that product formation is more efficient for NMP by an order of magnitude; the relative quantum yields were determined to be 1.0:0.08. The quantum yield for product formation for NMN and PC was measured to be 0.014 with the limiting quantum yield 0.036, a low value most likely due to efficient back electron transfer.

Synthesis of *p*-chloro-, *p*-methyl-, and *p*-methoxyphenylcyclopropane was accomplished by lithium aluminum hydride reduction of the appropriately substituted ethyl cinnamate.[11] *p*-Cyanophenylcyclopropane was made by cyanide exchange on *p*-chlorophenylcyclopropane with copper cyanide.[12] Oxidation potentials were measured versus a standard calomel electrode by cyclic voltammetry. Fluorescence quenching experiments were carried out and $k_q$(exptl) values were obtained from the slope of the Stern–Volmer plots $I/I_0 = 1 + k_q\tau$[quencher], where $I$ and

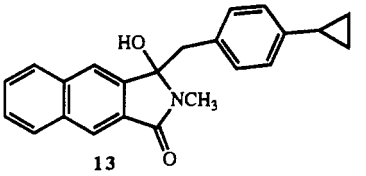
**Table I. NMN Fluorescence Quenching Data and Relative Quantum Yields of Product Formation for Various Phenylcyclopropanes**

| | MeO | Me | H | Cl | CN |
|---|---|---|---|---|---|
| $\Delta G_{Et}$ (kcal/mol) | −9.51 | −6.05 | −0.05 | 0.64 | 7.79 |
| $k_q$(calcd) × $10^{-10}$ ($M^{-1}$ $s^{-1}$) | 1.21 | 0.986 | 0.133 | 0.073 | $<10^{-5}$ |
| $k_q$(exptl) × $10^{-10}$ ($M^{-1}$ $s^{-1}$) | 1.94 | 1.20 | 0.089 | 0.051 | *b* |
| $E_{ox}$ (V) | 1.42 | 1.57 | 1.83 | 1.86 | 2.17 |
| $\Phi_{rel}$ | *c* | 0.56[a] | 1.00 | 0.85 | *c* |

[a] Includes all three products. [b] No quenching observed. [c] No reaction.

$I_0$ are the intensities of fluorescence with and without quencher, the $Y$-intercept is equal to one, and the slope is equal to $k_q\tau$. $\tau$ is the lifetime of the excited species, NMN, which has been determined to be 5.2 ns.[13] Values of $k_q\tau$ that are less than 0.2 $M^{-1}$ are considered below the practical limit of detection which corresponds to values of $k_q$ that are less than or equal to 3.7 × $10^7$ $M^{-1}$ $s^{-1}$ for NMN.

The relative quantum yields of product formation for the substituted phenylcyclopropanes were determined. Irradiation of NMN with *p*-cyano- or *p*-methoxyphenylcyclopropane afforded no products. *p*-Chlorophenylcyclopropane gave the expected products **9** and **10** (eq 4) in a 63% yield; however, *p*-methylphenylcyclopropane yielded three products, the spiro ethers **11** and **12** in a 32% yield and **13** in a 14% yield. The structure of **13** follows

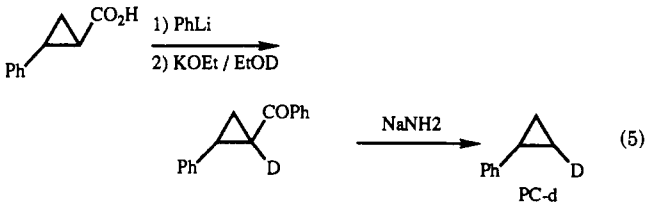



**13**

from its spectral characterization which showed a hydroxyl and an amide carbonyl in the IR spectrum. In addition to the aromatic protons, the $^1$H NMR spectrum showed two singlets at $\delta$ 6.74 and 3.24 due to the xylyl group and hydroxyl proton, respectively, doublets at $\delta$ 3.52 and 3.12 from the benzylic protons, and multiplets at $\delta$ 1.79–1.66, 0.90–0.80, and 0.58–0.50 corresponding to the cyclopropyl hydrogens.

*cis*-2-Deutero-1-phenylcyclopropane (PC-d) was chosen as a probe to determine whether the reaction occurred via a stepwise or concerted mechanism. By labeling one center with deuterium, relative stereochemistry is introduced, without markedly affecting the chemistry via steric effects, and conservation or loss of stereochemistry in the reaction pathway is reflected in the stereochemistry of the product formed. The synthesis of PC-d was carried out using a scheme designed by Berson and co-workers (eq 5).[14]

(11) Ouelette, R. J.; Robins, R. D.; South, A., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 1619.
(12) Friedman, L.; Schechter, H. *J. Org. Chem.* **1961**, *26*, 2522.
(13) Klingler, L. J. Ph.D. Thesis, University of Maryland, 1984.
(14) Berson, J. A.; Pedersen, L. D.; Carpenter, B. K. *J. Am. Chem. Soc.* **1976**, *98*, 122. Wood, J. T.; Arney, J. S.; Cortes, D.; Berson, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 3855.




(5)

Reaction of *trans*-2-carboxy-1-phenylcyclopropane with 2 equiv of phenyllithium gave *trans*-2-phenyl-1-benzoylcyclopropane in a 49% yield. Deuterium exchange was accomplished by treatment of the ketone with potassium ethoxide in ethanol-O-*d* followed by workup with $D_2O$ to give *trans*-1-deutero-2-phenyl-1-benzoylcyclopropane. Cleavage of the ketone using freshly prepared sodium amide gave the desired PC-d in a modest 40% yield with 81% deuterium incorporation.

There are two possible reactive complexes in which the phenylcyclopropyl radical cation ($PC^{\bullet+}$) can align itself with the imide radical anion ($NMN^{\bullet-}$). The anti reactive complex gives rise to the biradical **14a**, if the reaction is stepwise, which upon collapse yields cis-deutero-anti product **15a**. The syn reactive complex affords biradical **14c** and cis-deutero-syn product **15c**. Bond rotation is common in biradicals such as **14a** and **14c**. Rotation of biradical **14a** gives **14b** which collapses to trans-deutero-syn product **15b**, and in a similar fashion **14c** rotates to **14d** and affords trans-deutero-anti product **15d**.

Since approximately equal amounts of syn and anti product are observed in the reaction, both reactive complexes must be equally accessible, i.e., energetically equivalent. If the reaction were concerted, only cis-anti and cis-syn, **15a** and **15c**, would be observed. However, if attack proceeds in a stepwise manner, then either one or both reactive complexes could be involved and a number of combinations are possible. If anti orientation is favored exclusively, then only cis-anti and trans-syn products, **15a** and **15b**, will be formed, and, if only syn orientation is important, then cis-syn and trans-anti, **15c** and **15d**, would be the products. Free rotation must occur in either mechanism since both syn and anti adducts were observed. Finally if both reactive complexes are equally accessible and free rotation occurs, then the deuterium will be distributed equally among the four isomers; however, should free rotation be impeded, it would be impossible to distinguish between a stepwise and a concerted mechanism. All of these possibilities have been summarized in Table II.

It is important to realize that the $CH_2$ center and the CHD center of PC-d are equally vulnerable to nucleophilic attack by $NMN^{\bullet-}$ and only one center need be considered, although the data are identical. The stereochemistry of the deuterium was determined on pure syn and anti samples by integration of the two protons adjacent to the oxygen, $H_1$ and $H_2$, which occur at $\delta$ 4.63 and 4.41 versus the integration of the benzylic proton $H_5$ at $\delta$ 4.25. Fortunately, the exact assignments of $H_1$ and $H_2$ were not required to analyze the data (Table III).

## Discussion

The rate of fluorescence quenching for electron-transfer mechanisms can be calculated by the equations derived by Weller and Rehm (eq 6 and 7). It is generally assumed that when the experimental rate of quenching is within a factor of 2 of the calculated rate, electron transfer is occurring. As shown in Table I, the $k_q$(exptl) values all agree within a factor of 2 of $k_q$(calcd). This is seen as strong evidence that the interaction between excited imide and PC involves electron transfer. The anti-Markovnikov addition of methanol to PC which gave **4** and 1-phenyl-3-methoxypropane provides further evidence of an electron-transfer mechanism.[15] Interestingly, no cyclic products were seen in the reaction of NMP and PC in methanol, presumably because of hydrogen bonding of methanol to the imide which decreases its nucleophilicity.

**Scheme IV**

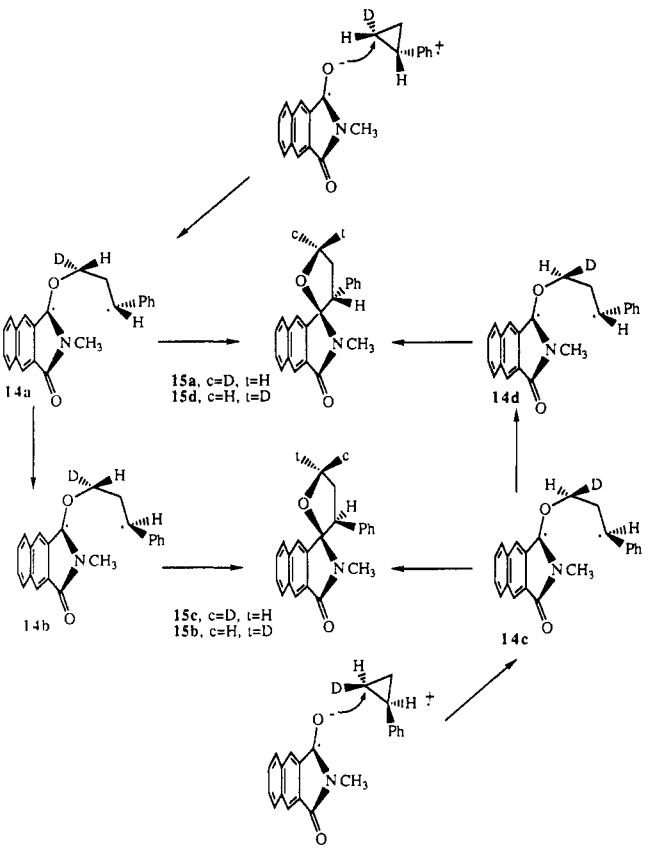



**Table II. Predicted Deuterium Distribution (%)**

| mechanism[a] | cis-anti **15a** | trans-anti **15d** | cis-syn **15c** | trans-syn **15b** |
|---|---|---|---|---|
| 1 | 50 (40)[b] | 0 | 50 (40) | 0 |
| 2a | 50 (40) | 0 | 0 | 50 (40) |
| b | 0 | 50 (40) | 50 (40) | 0 |
| 3a | 25 (20) | 25 (20) | 25 (20) | 25 (20) |
| b | 10 (8) | 40 (32) | 40 (32) | 10 (8) |

[a] Mechanisms: (1) concerted—both reactive complexes equally accessible; (2a) stepwise—anti orientation only, free rotation; (2b) stepwise—syn orientation only, free rotation; (3a) stepwise—both complexes equally accessible, free rotation; (3b) stepwise—syn:anti orientation preference = 1:4, free rotation. [b] Numbers in parentheses denote values adjusted for isotopic impurity.

**Table III. Percent Deuterium in 15**

| | anti | syn |
|---|---|---|
| $H_1$ | 20 | 20 |
| $H_2$ | 20 | 20 |

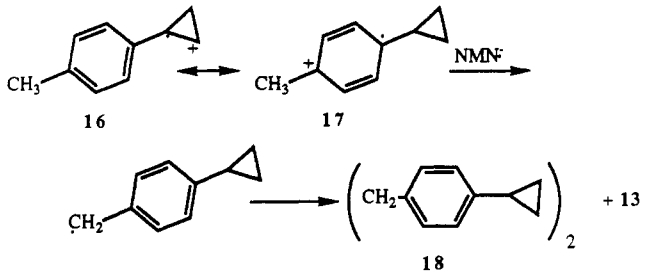
$$\Delta G^{\ddagger} = [(\Delta G/2)^2 + (\Delta G^{\ddagger}(0))^2]^{1/2} - \Delta G/2 \quad (6)$$

$$k_q = \frac{2\cdot 10^{10}}{1 + 0.25(\exp(\Delta G^{\ddagger}/RT) + \exp(\Delta G/RT))} \quad (7)$$

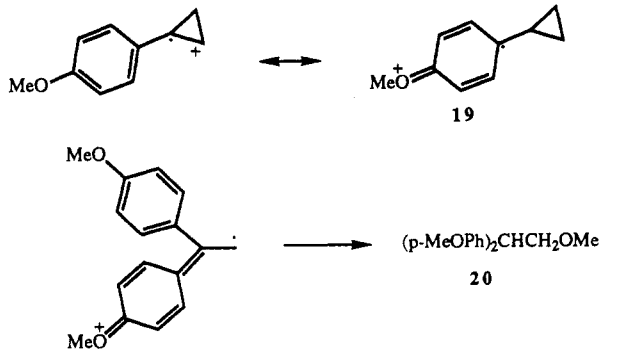
(15) Maroulis, A. J.; Shigemitsu, Y.; Arnold, D. R. *J. Am. Chem. Soc.* 1978, *100*, 535 and references therein. Stavinoha, J. L.; Mariano, P. S.; Leone-Bay, A.; Swanson, R.; Bracken, C. *J. Am. Chem. Soc.* 1981, *103*, 3148. Majima, T.; Pac, C.; Nakasone, A.; Sakurai, H. *J. Am. Chem. Soc.* 1981, *103*, 4499.

The relative quantum yields ($\Phi_{rel}$) of product formation for the substituted phenylcyclopropanes are also shown in Table I. As expected *p*-cyanophenylcyclopropane afforded no products because this reaction is extremely endothermic. A somewhat lower $\Phi_{rel}$ was observed for *p*-chlorophenylcyclopropane as predicted from the free energy of electron transfer which is slightly less favorable than for PC.

The formation of **13** can also be explained by an electron-transfer mechanism. Methyl substituents inductively stabilize cations; therefore, **17** represents a major contributing structure of the *p*-methylphenylcyclopropane radical cation **16**, making the methyl hydrogens more acidic and allowing the transfer of a proton to $NMN^{\bullet-}$, affording a radical pair which couples to give product **13**. Additionally, the benzyl radicals could diffuse out of cage and undergo coupling with one another to form bibenzyl **18**.[16]




The reaction of NMN with *p*-methoxyphenylcyclopropane gave no product, but this anomaly was not entirely unexpected. The positive charge of the radical cation **19** resides predominantly on the oxygen, making nucleophilic attack on this cyclopropane moiety less likely. Farid and Mattes observed a similar situation where the radical cation of 1,1-bis(*p*-methoxyphenyl)ethylene does not undergo nucleophilic attack by solvent to give **20**, presumably because the positive charge resides predominantly on the oxygen rather than on the ethylene carbon.[1] An alternative explanation is that reverse electron transfer is extremely rapid in these systems.




The results obtained from the deuterium-labeling experiment indicate that there is complete loss of relative deuterium stereochemistry. This is consistent with a stepwise mechanism where both reactive complexes are equally accessible and free rotation of the biradicals occurs. There is, however, another possible mechanism that would give rise to these data. Arnold and Wong have shown that 1,2-diphenylcyclopropane undergoes isomerization via an electron-transfer-mediated process when in the presence of an excited electron acceptor.[17] A similar process could occur between NMN and PC-d, destroying the stereochemistry. To eliminate this possibility, a solution of NMN and PC-d in perdeuteroacetonitrile was irradiated, and samples were analyzed by $^1H$ NMR at various intervals. The cyclopropyl proton signals are observed very far upfield and were easily analyzed in the mixture. Over a period of 6 h, no isomerization of PC-d was detected. Thus, loss of stereochemistry occurs only after nucleophilic attack on the phenylcyclopropane radical cation.

(16) Quinkert, G.; Opitz, K.; Weirsdorff, W. W.; Weinlick, J. *Tetrahedron Lett.* **1963**, 1863.
(17) Wong, P. C.; Arnold, D. R. *Tetrahedron Lett.* **1979**, 2101.

## Conclusion

The results presented in this study provide very strong evidence that the formation of the spiro tetrafuranyl lactams between PC and the aromatic imides NMP and NMN is an electron-transfer-mediated process. Other experiments have established that nucleophilic attack on the radical cation proceeds via a stepwise mechanism rather than a concerted one. The formation of these compounds represents one of the first examples of direct radical ion pair coupling. Investigations are continuing to determine the generality of this reaction, and studies have begun on the addition of 1,2-diphenylcyclopropane to NMN. These experiments should provide more information into the nature of radical ion pairs and their interactions.

## Experimental Section

**General.** Melting points were determined using a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 281 spectrophotometer and calibrated with the 1601-$cm^{-1}$ absorption band of polystyrene. NMR spectra were recorded on a Varian EM-360, IBM WP-200, or a Bruker AM-400 spectrometer. Elemental analysis were performed by Dr. Franz Kasler at the University of Maryland. Mass spectra were recorded on a 7070E-VG analytical high-resolution mass spectrometer or on a Hitachi RMU-6E low-resolution mass spectrometer. Fluorescence spectra and fluorescence quenching data were recorded on a Perkin-Elmer 204 fluorescence spectrophotometer. Irradiations were carried out in test tubes with a 450-W Hanovia medium-pressure mercury lamp.

Chromatographic separations were performed using flash column chromatography with silica gel (40–63 $\mu$) or alumina (grade 1) or a medium-pressure liquid chromatography (MPLC) system equipped with a silica gel (10–24 $\mu$) column. Analytical chromatographic separations were obtained using a Varian Model 5000 HPLC equipped with an ultraviolet-visible detector ($\lambda$ = 254 nm) and a silica gel SI-10, 36 cm × 4 mm column and interfaced to a Hewlett-Packard Model 5350A integrator printer. Analytical gas chromatography was carried out on a Hewlett-Packard Model 5350A GC equipped with a flame detector, a 3% Carbowax on Chrom W column (20 ft × 0.0075 in.).

**Photolysis of *N*-Methylphthalimide (NMP) and Phenylcyclopropane (PC) in Methanol.** A nitrogen-purged solution of NMP (300 mg, 1.86 mmol) and PC (3.54 g, 30.0 mmol) in 50 mL of methanol was irradiated for 27 h. The presence of 1-methoxy-3-phenylpropane was determined by comparison of GLC retention time with that of an authentic sample.

Methanol was removed in vacuo from the reaction solution and the crude material separated via MPLC (35% ether; 65% Skelly F) to give 135 mg (23.3%) of **4** which was recrystallized from ether. Pure product showed: mp 172–175.5 °C; IR ($CHCl_3$) 3540–3140 (br), 1685 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.78–7.74 (d, 1 H, $J$ = 8.3 Hz), 7.61–7.53 (m, 2 H), 7.09–6.91 (m, 3 H), 6.48–6.43 (m, 2 H), 4.30 (s, 1 H), 3.47–3.39 (dd, 1 H, $J$ = 11.4 Hz, $J$ = 0.3 Hz), 3.26 (s, 3 H), 3.29–3.19 (m, 1 H), 3.16–3.04 (m, 1 H), 2.82–2.69 (m, 1 H), 2.68 (s, 3 H), 2.09–1.92 (m, 1 H). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.27; H, 6.80; N, 4.50. Found: C, 73.26; H, 6.84; N, 4.40.

**Photolysis of NMP and PC in Acetonitrile.** A solution of NMP (322 mg, 2 mmol) and PC (4 mL, 30 mmol) in 40 mL of acetonitrile were irradiated at 0 °C for 4 h through a Pyrex filter under a nitrogen atmosphere. The reaction mixture was evaporated in vacuo and the residue chromatographed by HPLC. The separation of **5** and **6** was realized by using a Zorbax sil column and a methylene chloride–ethyl ether gradient programmed from

100% $CH_2Cl_2$ to 80% $CH_2Cl_2$:20% $Et_2O$ over 30 min. Compound **5** (2',3',4'-trihydro-4'-phenylfuran-1-oxospiroisoindolone) was isolated in 10% (4 mg) yield: $\nu_{max}$ 1700, 1390, 910 $cm^{-1}$; $^1H$ NMR d 2.55 (m, 1 H), 2.78 (s, 3 H), 2.85 (m, 1 H), 4.08 (q, $J$ = 11.5 Hz, $J$ = 8.5 Hz, 1 H), 4.30 (m, 1 H), 4.58 (t, $J$ = 8.5 Hz, 1 H), 6.76 (d, 2 H), 7.13 (d, 3 H), 7.54 (t, 1 H), 7.63 (bs, 2 H), 7.73 (d, 1 H); $^{13}C$ NMR (d 25.7, 30.0, 52.1, 69.0, 99.7, 121.6, 123.3, 126.7, 126.7, 127.6, 128.5, 129.7, 132.2, 132.4, 135.2, 147.2, 167.3; CIMS (M + 1) 280. $C_{18}H_{17}NO_2$ requires 279.1622. (Found C, 77.99; H, 6.0; N, 4.97 requires C, 77.44; H, 6.13; N, 5.05%). Compound **6** was isolated in 11% (4 mg) yield, $\nu_{max}$ 1700, 1390, 910 $cm^{-1}$; $^1H$ NMR d 2.60 (m, 1 H), 3.0 (m, 1 H), 3.20 (s, 3 H), 3.90 (m, 1 H), 4.35 (m, 1 H), 4.45 (m, 1 H), 6.96 (d, 2 H), 7.00 (m, 3 H), 7.20 (m, 3 H), 7.65 (d, 1 H); CIMS (M + 1) 280 ($C_{18}H_{17}NO_2$ requires 279.1622). NMP (297 mg) was recovered.

**Photolysis of *N*-Methyl-2,3-naphthalimide (NMN) and PC in Acetonitrile.** A solution of NMN (300 mg, 1.42 mmol) and PC (3.5 g, 30 mmol) in 50 mL of acetonitrile was irradiated in a Pyrex tube for 9 h. Solvent was removed in vacuo and the crude mixture separated by MPLC (35% ether; 65% Skelly F). NMN (165 mg) was recovered and 119 mg (57%) of a mixture of **7** and **8** was isolated. **7** showed: mp 205–208 °C; IR ($CHCl_3$) 1690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.08 (s, 1 H), 7.83 (t, 2 H, $J$ = 8.7 Hz), 7.70 (s, 1 H), 7.53–7.46 (m, 2 H), 7.17–7.09 (m, 2 H), 6.96–6.90 (m, 1 H), 6.81 (d, 2 H, $J$ = 7.4 Hz), 4.54 (t, 1 H, $J$ = 8.4 Hz), 4.44–4.38 (m, 1 H), 4.01–3.96 (dd, 1 H, $J$ = 12.8 Hz, $J$ = 6.8 Hz), 3.29 (s, 3 H), 3.12–3.02 (m, 1 H), 2.68–2.59 (m, 1 H). **8** showed: mp 176–180 °C; IR ($CHCl_3$) 1690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.29 (s, 1 H), 8.08 (s, 1 H), 8.04–7.98 (dd, 2 H, $J$ = 16.3 Hz, $J$ = 8.1 Hz), 7.66–7.60 (m, 2 H), 7.17–7.09 (m, 3 H), 6.99 (d, 2 H, $J$ = 4.3 Hz), 4.63 (t, 1 H, $J$ = 8.2 Hz), 4.44–4.38 (m, 1 H), 4.28–4.23 (dd, 1 H, $J$ = 13.6 Hz, $J$ = 7.4 Hz), 2.91–2.82 (m, 1 H), 2.81 (s, 3 H), 2.68–2.59 (m, 1 H). Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found for mixture: C, 80.00; H, 5.81; N, 4.11. MS for mixture (high resolution): observed mass (M) = 329.1427, $C_{22}H_{19}NO_2$ requires mass (M) = 329.1439.

**Photolysis of NMN and *p*-Chlorophenylcyclopropane in Acetonitrile.** A solution of NMN (250 mg, 1.18 mmol) and *p*-chlorophenylcyclopropane (3.6 g, 24 mmol) in 50 mL of acetonitrile was irradiated in a Pyrex tube for 9 h. Solvent was removed in vacuo and the crude mixture separated by MPLC (35% ether; 65% Skelly F). NMN (84 mg) was recovered and 164 mg (63%) of a mixture of **7** and **8** was isolated. **7** showed: mp 215.5–218 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 8.11 (s, 1 H), 7.88–7.82 (dd, 2 H, $J$ = 18.8 Hz, $J$ = 7.9 Hz), 7.70 (s, 1 H), 7.56–7.47 (m, 2 H), 6.97 (d, 2 H, $J$ = 6.8 Hz), 6.92 (d, 2 H, $J$ = 8.7 Hz), 4.53 (t, 1 H, $J$ = 8.3 Hz), 4.44–4.36 (m, 1 H), 3.97–3.92 (dd, 1 H, $J$ = 13.3 Hz), 3.27 (s, 3 H), 3.15–3.06 (m, 1 H), 2.69–2.60 (m, 1 H). **8** showed: mp 191–194.5 °C; IR ($CHCl_3$) 1690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.29 (s, 1 H), 8.09 (s, 1 H), 8.05–7.98 (dd, 2 H, $J$ = 21.5 Hz, $J$ = 8.3 Hz), 7.70–7.59 (m, 2 H), 7.09 (d, 2 H, $J$ = 8.3 Hz), 6.72 (d, 2 H, $J$ = 8.6 Hz), 4.63 (t, 1 H, $J$ = 8.5 Hz), 4.44–4.36 (m, 1 H), 4.23–4.18 (dd, 1 H, $J$ = 13.3 Hz, $J$ = 7.4 Hz), 2.87–2.82 (m, 1 H), 2.82 (s, 3 H), 2.69–2.60 (m, 1 H). MS for mixture (high resolution): observed mass (M: $^{37}Cl$) = 365.0972, $C_{22}H_{18}ClNO_2$ requires (M: $^{37}Cl$) 365.0996.

**Photolysis of NMN and *p*-Methylphenylcyclopropane in Acetonitrile.** A solution of NMN (250 mg, 1.18 mmol) and *p*-methylphenylcyclopropane (3.13 g, 24 mmol) in 50 mL of acetonitrile was irradiated in a Pyrex tube for 9 h. The solvent was removed in vacuo and the crude mixture separated by MPLC (35% ether; 65% Skelly F). NMN (32 mg) was recovered and 112 mg (32%) of a mixture of **11** and **12** and 51 mg (14%) of **13** were isolated. **11** showed: mp 193.5–194.5 °C; IR ($CHCl_3$) 1690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.10 (s, 1 H), 7.86–7.82 (m, 2 H), 7.72 (s, 1 H), 7.54–7.44 (m, 2 H), 6.88 (d, 2 H, $J$ = 8.0 Hz), 6.79 (d, 2 H, $J$ = 8.0 Hz), 4.52 (t, 1 H, $J$ = 8.4 Hz), 4.43–4.35 (m, 1 H), 3.87–3.82 (dd, 1 H, $J$ = 13.0 Hz, $J$ = 6.6 Hz), 3.28 (s, 3 H), 3.17–3.07 (m, 1 H), 2.67–2.56 (m, 1 H), 2.07 (s, 3 H). **12** showed: mp 185.5–186.5 °C; IR ($CHCl_3$) 1690 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.28 (s, 1 H), 8.03 (s, 1 H), 8.04–7.98 (dd, 2 H, $J$ = 17.8 Hz, $J$ = 8.0 Hz), 7.65–7.57 (m, 2 H), 6.90 (d, 2 H, $J$ = 8.0 Hz), 6.67 (d, 2 H, $J$ = 8.0 Hz), 4.62 (t, 1 H, $J$ = 8.2 Hz), 4.43–4.35 (m, 1 H), 4.23–4.18 (dd, 1 H, $J$ = 13.5, $J$ = 7.3 Hz), 2.89–2.80 (m, 1 H), 2.81 (s, 3 H), 2.67–2.56 (m, 1 H), 2.22 (s, 3 H). MS for mixture **11** and **12** (high resolution): observed mass (M) = 343.1551, $C_{23}H_{21}NO_2$ requires (M) 343.1572. **13** showed: mp 119–131 °C dec; IR ($CHCl_3$) 3700–3240, 1680 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.89 (s, 1 H), 7.82–7.70 (m, 2 H), 7.63 (s, 1 H), 7.57–7.43 (m, 2 H), 6.74 (s, 4 H), 3.52 (d, 1 H, $J$ = 14.0 Hz), 3.24 (s, 1 H), 3.12 (d, 1 H, $J$ = 14.0 Hz), 3.04 (s, 3 H), 1.79–1.66 (m, 1 H), 0.90–0.80 (m, 2 H), 0.58–0.50 (m, 2 H). MS (high resolution): observed mass (M – $H_2O$) = 325.1445, $C_{23}H_{19}NO$ requires (M – $H_2O$) 325.1466.

**Oxidation Potential of PC and Para-Substituted Phenylcyclopropanes.**[18] The oxidation potential of various phenylcyclopropanes were determined using a Bio-Analytical Systems electrochemical analyzer, Model BAS-100, equipped with a Houston Instruments digital plotter, Model DMP-40; 200 mV $s^{-1}$ scans were taken. The oxidation potential was measured using a gold electrode (area = 0.0201 $cm^2$) as the working electrode, a platinum wire as the auxillary electrode, and a saturated calomel electrode (SCE) as the reference electrode. A solution of approximately $1:10^{-3}$ M phenylcyclopropane and 0.1 M tetraethylammonium perchlorate (TEAP) in acetonitrile (distilled over calcium hydride) was used. The oxidation potential of each compound was obtained from the irreversible cyclic voltammograms. Under the exact same conditions, the reduction potential of naphthalimide was observed at –1.72 V. The literature value is –1.65 V when platinum was used as a working electrode.[2e]

**X-ray Crystallographic Investigation of 8**: colorless crystals from ethyl ether; 0.2 × 0.3 × 0.36 mm specimen used for diffraction experiments; Enraf-Nonius CAD4 diffractometer; Mo radiation with incident beam graphite monochromator (K$\alpha$ $\lambda$ = 0.710 69 Å); monoclinic space group, $P2_1/n$; cell parameters from 25 reflections centered in the range 11.5 ≪ 17.5°; $a$ = 7.140 (1), $b$ = 14.038 (1), $c$ = 16.729 (3) Å, $\beta$ = 97.28 (1)°; $\rho$ calcd = 1.188 g $cm^{-3}$ for $Z$ = 4; $C_{22}H_{19}NO_2$ mol wt of 297.4; $2\theta$–$\theta$ scan at variable speed of $\theta$ = 1.27–8.24° $min^{-1}$; $\theta$ scan range of 1.5 × (1.08 + 0.34 tan $\theta$)°; data collection range of $\theta$ = 1–25° for $h$ = –9, $k$ = 0 to 17, $l$ = –20 to 0; 3239 total data measured. Six standard intensities measured every 2 h of X-ray exposure showed an average decline of 0.5%, no decay correction applied; 3071 unique data; 1671 data with $I \geq 3\sigma(I)$; $R_{sym}$(on F) = 0.003 for 107 reflection pairs. All crystallographic calculations performed with the TEXSAN program system[19] on a DEC MicroVax II computer; structure solved with the MITHRIL direct methods link;[20] refinement by full-matrix least-squares with anisotropic temperature factors for C, O, and N and isotropic terms for H; $\sum w(F_o - F_c)^2$ minimized; $w = 1/\sigma^2(F_o)$; secondary isotropic extinction parameter refined; final $R$ factor = 0.040, weighted $R$ = 0.041; goodness-of-fit = 1.35; minimum and maximum values in final difference electron map of –0.14 and 0.14 e $Å^{-3}$. Atom coordinates, temperature factors, and structure factor data have been deposited as supplementary material.

**Fluorescence Quenching of NMN.** Five solutions were prepared containing $2 \times 10^{-4}$ M NMN and varying concentrations of quencher ($10^{-3}$ to $10^{-2}$ M) in spectral grade acetonitrile. The excitation wavelength was 315 nm and the emission was observed at the second maximum, 388 nm. Fluorescence data were analyzed using the Stern-Volmer relationship:

$$I_0/I = 1 + k_q\tau[\text{quencher}]$$

where, $I_0$ and $I$ are the intensities of fluorescence in the absence of quencher and in the presence of quencher, respectively, $k_q$ is the rate constant for quenching, and $\tau$ is the singlet lifetime of NMN. A plot of $I_0/I$ versus the concentration of quencher was linear and had a correlation greater than 0.99 and an intercept of 1. Using the value estimated for $\tau$, 5.2 ns, $k_q$ was determined.

**Relative Quantum Yields of Photoaddition of PC to NMP and Photoaddition to NMN.** Ten milliliter solutions of 0.028 M NMN and 0.59 M PC were irradiated for 10 h on a merry-go-round apparatus. One milliliter of the NMP solution was

(18) This work was assisted by Ms. Rosanne Kannuck under the direction of Dr. Richard Durst at the Organic Electrochemistry Laboratory at the National Institute of Standards and Technology, Gaithersburg, MD.

(19) TEXSAN. TEXRAY Structure Analysis System, Version 1.5, 1985, Molecular Structure Corp., The Woodlands, TX.

(20) Gilmore, C. J. MITHRIL: A Computer Program for the Automatic Solution of Crystal Structures, University of Glasgow: Glasgow, Scotland, 1983.

removed and combined with 1 mL of standard solution ($1.32 \times 10^{-4}$ M benzamide (internal standard) in methylene chloride), and 1 mL of NMN solution was removed and combined with 1 mL of second standard solution ($1.32 \times 10^{-3}$ M benzamide in methylene chloride); analysis was by HPLC (75% or 35% ether/Skelly F; 3.5 mL/min). Only the syn isomers **6** and **8** were examined. The relative quantum yields for NMP and NMN were determined to be 0.08 and 1.0, respectively.

**Relative Quantum Yields of Photoaddition of Substituted Phenylcyclopropanes to NMN.** Five milliliter solutions containing 0.028 M NMN and 0.59 M PC, *p*-chlorophenylcyclopropane, or *p*-methylphenylcyclopropane in acetonitrile were irradiated in parallel for 10 h on a merry-go-round. Aliquots were analyzed as outlined above.

**Quantum Yield of Photoaddition of PC to NMN.** Six milliliter solutions of 0.028 M NMN and 0.59 M PC were placed in a quartz cell, degassed, and irradiated at 360 nm for 8 h using a high-pressure mercury lamp in a black box apparatus. Aliquots were removed and analyzed as above. Einsteins of light were determined by standard ferrioxalate actinometry[21] before and after each run.

(21) Hatchard, G. C.; Parker, C. A. *Proc. R. Soc. (London), Ser. A* **1956**, *235*, 518 and references therein.

**Limiting Quantum Yields of PC Photoaddition to NMN.** Ten milliliter solutions of 0.028 M NMN and varying concentrations of PC (0.30–1.48 M) were irradiated for 9 h on a merry-go-round apparatus. Aliquots were analyzed as above. The relative quantum yields were normalized to the absolute quantum yields and plotted $1/\Phi$ versus $1/[PC]$ to determine the limiting quantum yield.

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**Registry No.** **4**, 125928-12-3; **5**, 104506-74-3; **6**, 104506-73-2; **7**, 104506-76-5; **8**, 104506-75-4; **9**, 125928-13-4; **10**, 125928-14-5; **11**, 104506-78-7; **12**, 104506-77-6; **13**, 104506-79-8; PC, 873-49-4; NMP, 56788-11-5; NMN, 42896-23-1; *p*-methoxphenylcyclopropane, 4030-17-5; *p*-methylphenylcyclopropane, 6921-43-3; *p*-chlorophenylcyclopropane, 1798-84-1; *p*-cyanophenylcyclopropane, 1126-27-8.

**Supplementary Material Available:** Atom coordinates and temperature factors for 8 (1 page); structure factors for 8 (12 pages). Ordering information is given on any current masthead page.

# Theoretical Study of the Hydroxyl Nucleophilic Attack on the 6-Aminopyrimidine Molecule: Functional Implications in the Reaction Mechanism of Nucleoside Deaminative Enzymes

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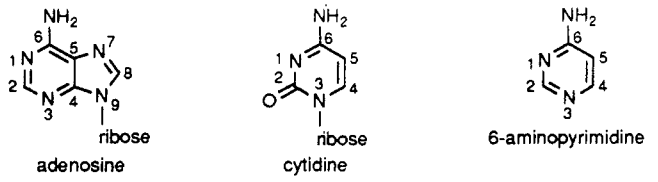
A quantum chemical study of hydroxyl attack on a reduced model of adenosine and cytidine has been performed by using both semiempirical MNDO and ab initio 4-31G methodologies. Because the studies on the reaction pathways were carried out by using semiempirical methods, the validity of MNDO for the study of such reactions was tested first. For this purpose, hydroxyl attack on the formaldehyde molecule (a well-known and documented reaction similar to the reaction of interest) was considered. Results obtained from the study of this reaction at the MNDO level were consistent with both ab initio 6-31+G* results and experimental data. The study of hydroxyl attack on the 6-aminopyrimidine molecule reveals the existence of two reactions: the first consists of proton capture by the hydroxyl of the amine hydrogen trans to N1, while the second consists of the formation of a Meisenheimer complex by means of hydroxyl attack at C6. Ab initio and semiempirical "static" reactivity parameters point to the first reaction as being favored over the second if no restrictions are imposed on the hydroxyl attack pathway. The imposition of orientation restrictions on the hydroxyl attack results in feasible "reactive pathways" that are almost perpendicular to the molecular plane and that lead to the Meisenheimer complex formation with a very low energy barrier. The biochemical implications of the results obtained on the mechanism of the reaction of both adenosine and cytidine deaminases are extensively discussed in the context of previous theoretical and experimental data. Finally, several possible "microscopic" reaction mechanisms for these enzymes are suggested.

## Introduction

Adenosine deaminase (ADA EC 3.5.4.4) and cytidine deaminase (CDA EC 3.5.4.5), which catalyze the conversion of adenosine to inosine and of cytidine to uridine, respectively, are probably the most important and well-known deaminative enzymes. In recent years, the reaction mechanisms of both ADA and CDA have been extensively studied, not only because of the biological relevance of these enzymes but also from a pharmacological point of view, as their substrates and inhibitors are currently used as antineoplasic, antihypertensive, antimetabolic, antiviral, and antibiotic agents.[1-9]

**Scheme I**

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