Effects of Stereochemistry on the Rates of Hydrogen–Deuterium Exchange of Protons α to the Nitrosamino Group

Robert R. Fraser* and L. K. Ng

Contribution from the Department of Chemistry, University of Ottawa, Ottawa, Canada, K1N 6N5.

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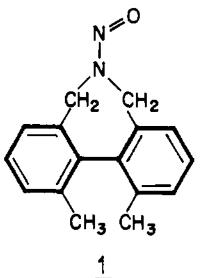
Abstract: Measurement of the rates of exchange of the four benzylic protons of the rigid dibenzazepine **1** were made in *tert*-butyl alcohol-*O-d* containing potassium *tert*-butoxide at several concentrations. Each pseudoaxial proton exchanged 100-fold faster than its geminal partner (pseudoequatorial), likely as a result of a stereoelectronic effect. Each syn proton exchanged 1000-fold faster than the anti proton in the same biaryl environment. The lack of any significant effect of added crown ether on the rate of exchange of either a syn or an anti proton indicates lack of involvement of the counterion. A suggested explanation for the unusual preference for syn exchange in this work is based on the symmetry properties of the anionic intermediate. This intermediate, like butadiene dianion, has an attractive interaction between the terminal atoms of the four-atom π system in the highest occupied molecular orbital (HOMO). This explanation is similar to that of Epiotis and co-workers, which accounts for the well-established preferential stability of cis over trans dihalo and dialkoxy ethylenes.

We recently reported that the four benzylic protons in the bridged biaryl nitrosamine **1** underwent markedly different rates of base-catalyzed H–D exchange in *tert*-butyl alcohol-*O-d*.[1] It was notable that each proton syn to the oxygen exchanged faster than those anti and that the axial-like protons exchanged more rapidly than those in an equatorial-like environment. Due to the approximate nature of these data[2] we have sought and obtained more accurate rates which reveal much larger selectivities than originally estimated, exchange syn vs. anti to the nitroso oxygen being favored 1000-fold and exchange "axial" vs. "equatorial" being favored 100-fold. Additional experiments provide evidence pertaining to the origin of the observed stereoselectivities and in view of the subsequent extensive demonstration[3] that anions α to the nitrosamine group react with a variety of electrophiles in good yield, thereby providing a new method of substitution adjacent to nitrogen, an expansion of our understanding of the behavior of these anions becomes of practical importance.



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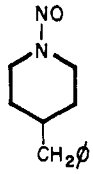

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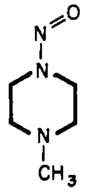

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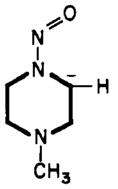

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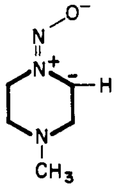

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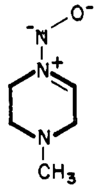

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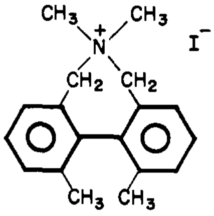

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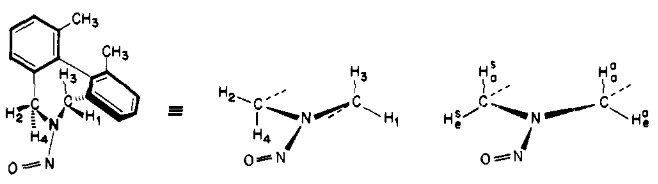
The conformationally rigid nitrosamine, *N*-nitroso-6,7-dihydro-1,11-dimethyl-5*H*-dibenz[*c,e*]azepine (**1**), was chosen for this study. Because rotation about the central biaryl bond is prevented by the methyl groups in positions 1 and 11[4] and rotation about the N–N bond is slow,[5] the four protons α to the nitrosamino function are magnetically nonequivalent. In the 100-MHz NMR spectrum of **1** in $CDCl_3$, four doublets appear for the four α protons at τ 4.546 (H_1), 4.588 (H_2), 5.250 (H_3), and 6.591 (H_4). The inequality in geminal coupling constants, $J_{1,3} = 13.5$ Hz and $J_{2,4} = 14.9$ Hz, identified the diastereotopic pairs. Further assignments were made in analogy with those of Chow and Colon[6] for the α protons of *N*-nitroso-4-benzylpiperidine (**2**). It can be seen in Figure 1, depicting the three-dimensional formulas for **1** and **2**, that the α protons in **1** and **2** have almost identical dispositions with respect to the nitrosamino group. Because of these similarities in geometry, the shifts for H_2, H_3, and H_4 relative to H_1 are very close to those observed for the α protons of **2**. Since H_3 and H_4 occupy environments which are almost the same as those occupied by the axial protons of **2**, we will refer to H_3 and H_4 as being ψ-axial. For the same reason H_1 and H_2 are considered to be ψ-equatorial.

These assignments were confirmed in two ways. The observed magnitudes ($H_2 = 1.34 > H_4 = 0.93 > H_1 = 0.56 > H_3 = 0.53$ ppm) of the downfield shifts induced by the addition of $Eu(dpm)_3$ to a solution of **1** in CCl_4 is consistent with the above assignment in view of their established distance dependence.[7] For further confirmation, a sample selectively deuterated at H_4 was observed to undergo equilibration (via NNO rotation) with the label appearing at H_3 until equal intensities of H_3 and H_4 were attained. This demonstrates H_3 and H_4 to be in the same environment, with respect to the biaryl skeleton, as the above assignment demands.

Barrier to Rotation about the N–N Bond in 1. Nitrosamines are known to possess large barriers to rotation about the N–N bond, usually in the range of 21–26 kcal/mol.[5] Since rotation about the N–N bond of **1** is finite at 27° and it interchanges the environment of H_1 and H_2 and H_3 and H_4, it was important to measure this barrier as accurately as possible. Furthermore, the possibility that the rate of rotation could be catalyzed by strong base had to be examined, since rotation via the anion of **1** might well be a lower energy process.[8] For this reason the barrier to rotation in **1** was determined in *tert*-butyl alcohol-*O-d* and in 0.009 M and 0.2 M solutions of potassium *tert*-butoxide in *tert*-butyl alcohol-*O-d*. The results of intensity



1

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Figure 1. A three-dimensional representation of the protons α to the nitrosamino function in **1** and **2**.

Table I. Rate of Rotation about N-N Bond in **1**

Run	Base[a] concn, M	Proton monitored	$10^5 k$,[b] s^{-1}
1	0.0	H_4	9.9 ± 0.3 (0.999)
2	0.009	H_3	9.6 ± 0.3 (0.997)
3	0.20	H_1	9.7 ± 0.2 (0.993)

[a] The base used was potassium *tert*-butoxide in *tert*-butyl alcohol-*O*-*d* solvent. [b] Rate constants obtained by least-squares analyses are quoted with the uncertainty in accuracy equal to the standard deviation of slope. Correlation coefficients, in parentheses, follow. All measurements made at probe temperature of our HA-100 spectrometer, 27 °C.

measurements at appropriate intervals using an HA-100 NMR spectrometer gave the results listed in Table I. Since each rate constant was obtained by monitoring a different absorption peak, we will describe each measurement in some detail. For run 1, a sample selectively deuterated at H_4 was prepared by allowing exchange in 0.006 M *tert*-butoxide-*tert*-butyl alcohol-*O*-*d* to proceed for 6 min. Quenching with acid followed by rapid isolation and redissolution gave a sample containing 67% deuterium at H_4 and 20% at H_3. The redistribution of this label to the equilibrium value was monitored by NMR integral measurements.

For run 2, the concentration of base (0.009 M) was chosen so that, although H_4 and some H_2 undergo base-catalyzed exchange, H_3 can be considered inert. Since H_3 exchanges about tenfold slower than H_2 and H_2 exchanges very slowly ($t_{1/2}$ = 10 h) at still higher base strength (0.012 M), this inertness of H_3 is established. As a consequence, the rate of deuteration measured at H_3 after H_4 has completely exchanged (30 min) reflects the rate of rotation only. A correction for the proton content of the solvent pool was made as described in the Experimental Section.

For run 3, it is assumed that at 0.2 M concentration of base any deuteration at H_1 occurs via rotation only. The observation that the half-life for exchange of H_1 is 19 h in presence of 0.6 M base validates this assumption. The rate measurements were conducted by monitoring the total integral of H_1 and residual H_2. A correction for the proton content of the solvent pool was again made.

As Table I shows, the rates of rotation do not change appreciably with increasing concentration of potassium *tert*-butoxide, but are equal within the limits of accuracy of measurement (±4%). The average value for the first-order rate constant is $9.7 \times 10^{-5}\ s^{-1}$, from which one can calculate a free energy barrier to rotation of 23.2 kcal/mol (at 27 °C). This barrier equates to a half-life for rotation of 120 min.

Determination of Base-Catalyzed H-D Exchange Rates. The base-catalyzed H-D exchange of each diastereotopic proton in **1** was monitored by integral measurements of each proton at periodic intervals using an HA-100 NMR spectrometer. Since a finite amount of rotation occurs during the interval of study (except for H_4, whose half-life during exchange was 3 min), a correction factor must be included. Consider the exchange rate for the process $H_3 \rightarrow D_3$. The conversion $H_3 \rightarrow D_3$ takes place by chemical exchange and also via rotation about the partial N-N double bond, i.e., $H_3 + D_4 \rightarrow H_4 + D_3$. At the concentration of base employed (0.15 M) any H_4 is instantaneously replaced by deuterium and so $[D_4]$ remains constant. Thus, the rate of deuteration at H_3 via the rotation process = $k_{rot}[H_3]$.

For base-catalyzed chemical exchange, the rate = $k_{chem}[H_3][B]$ = $k'_{chem}[H_3]$, where k'_{chem}, the pseudo-first-order rate constant, = $k_{chem}[B]$ and the observed rate = $k_{obsd}[H_3]$, which is the sum of the two contributing processes, i.e., $k_{obsd} = k'_{chem} + k_{rot}$. The same situation prevails during the measurement of the exchange of H_1, since H_2 remains completely deuterated during the experiment.

In the determination of the rate constant for exchange of H_2 a still different treatment was used. In run 4, integral measurement of the overlapping absorption regions of H_1 and H_2 were taken. As a result, the effect of rotation does not alter the total deuterium uptake in this spectral region. It does effectively double the quantity of H_2 available for exchange, but this effect is negligible since the exchange of H_2 was only followed to 20% completion.

The rates of chemical exchange of the benzylic protons at several base concentrations are summarized in Table II. The observed rates, when different from chemical rates, are given also. In run 4 the very large difference in the rates of exchange of H_4 vs. H_2 restricts the accuracy of their measurement. Although the rate of exchange of H_4 would be more accurate at lower base concentration, there is a finite danger that at extremely low concentrations of base some quenching of base by small amounts of impurities can occur. The rates obtained in run 4 are estimated to be accurate to only ±20%, giving a value for the ratio k_4/k_2 of between 170 and 370:1. The remaining rate data is considerably more accurate. In fact, the next poorest in accuracy involves the exchange rate of H_1 in run 6. The standard deviation in this rate constant derived from a least-squares analysis is ±6%. All in all it would seem wise to deduce from all the data that protons H_1-H_4 have rate constants of relative orders of magnitude, $1{:}10^3{:}10^2{:}10^5$.

Effects of Stereochemistry on the Relative Rates. In the nitrosamine under study, the orientation of the four benzylic protons with respect to the activating N-NO group can be categorized according to two criteria: (a) orientation with respect to the π orbitals of the N-N=O function, i.e., H_4 and H_3 are said to be ψ-axial, H_2 and H_1 ψ-equatorial; and (b) orientation relative to the nitroso oxygen atom, i.e., H_4 and H_2 are syn to oxygen, while H_3 and H_1 are anti. From the data in Table I it can be seen that each ψ-axial proton exchanges much faster than its diastereotopic partner (roughly 100-fold in each case). The syn vs. anti factor can be seen to be even larger in that both syn protons exchange 1000-fold faster than their anti partners.

In any consideration of factors affecting the rates of H-D exchange, certain simplifying assumptions can be justifiably made. In the exchanges in question, we will assume that the relative rates of H-D exchange reflect the relative ease of carbanion formation,[9] i.e., that our kinetic acidity data obeys the Bronsted relation and thus the relative energies of the transition states for each isotopic exchange are directly proportional to the thermodynamic acidities of the anions being formed.

The possibility that internal return[11] as well as isotope drowning[12] might compete with deuteration of the carbanion, thereby negating this assumption, is considered improbable. Two observations support this statement. First, the sole product obtained by formation of the anion of **1**, using lithium diisopropylamide in THF at −78 °C followed by methylation with methyl iodide (also at −78 °C), was the monomethyl derivative in which the methyl was ψ-axial and syn.[13] It would seem reasonable that the preference for an electrophilic substitution

Table II. Rates of Exchange of Protons in **1**

Run	Base,[a] M	Proton	$10^5 k_{obsd}$,[b] s^{-1}	$10^5 k_{chem}$, s^{-1}	Relative rates
4	0.012	H_4	430 ± 80	440	10^5
		H_2		1.8 ± 0.3 (0.935)	
5	0.15	H_3	33 ± 1 (0.995)	24	
		H_2		264 ± 6 (0.999)	10^3
6	0.60	H_3	105 ± 0.15 (0.999)	96	10^2
		H_1	11.1 ± 0.7 (0.975)	1.4	1

[a] Base was potassium *tert*-butoxide in *tert*-butyl alcohol-*O*-*d*. [b] Rate constants obtained by least-squares analysis are quoted ± the standard deviation and the correlation coefficient appears in parentheses. Values given represent pseudo-first-order rate constants.

axial and syn in both THF and *tert*-butyl alcohol-*O*-*d* reflects involvement of the same anion-stabilizing effects in both media. Since "internal return" and "isotope drowning" cannot be involved in the methylation in THF, they most probably are not of influence in the exchange reaction either. Second, the findings (to be given in detail below) that addition of dicyclohexyl-18-crown-6 had only minor effects on the rates of exchange of H_2 and H_3 supports the contention as well. In cases known to involve "internal return" and "isotope drowning" the effects of added crown ether on both absolute and relative rates have been very large.[14] It then follows that the exchange rate of a ψ-axial vs. a ψ-equatorial proton is a measure of the difference in activation energies for the two proton abstractions.

ψ-Axial vs. ψ-Equatorial Selectivity. The first reported observation of H-D exchange α to a nitrosamino group was made by Keefer and Fodor[15] using *N*-nitroso-*N'*-methylpiperazine (**3**). They suggested as a tentative explanation for the discovered lability of the α protons that the positive charge on the ring nitrogen provided "ylide"-type stabilization of the anionic intermediate (e.g., resonance structures **4a** and **b** are sufficient to describe the electron distribution in the anion). In the preliminary report of this work we pointed out the possibility that **4c** might also be considered as contributing to the stability of the anion. This structure involves an allylic-type delocalization. Intuitive objections to its consideration on the basis of juxtaposition of partial negative charges should be tempered by consideration of the strong solvation present in the hydroxylic solvents used for the exchange.[16] Compound **1** was chosen for this study since the orientation of the ψ-axial and ψ-equatorial protons differ markedly with respect to the adjacent π system, as shown in Figure 1.

In the course of pseudoaxial proton abstraction (see Figure 1a) the developing carbanion is properly oriented for overlap with the partial N-N double bond of the nitrosamino group. Such overlap is severely restricted in the carbanion being formed by pseudoequatorial proton abstraction (Figure 1b). The magnitude of this will naturally depend upon the difference in anion orientation in the transition states. As House has explained,[17] in enolate reactions the competitive transition states differ little in geometry from the enolates and so one sees little preference for axial attack. For example, a small degree of stereoselectivity was recently observed in exchange of the α protons of 4-*tert*-butylcyclohexanone[18] (k_{ax}/k_{eg} = 5:1). We attribute the much larger selectivity in **1** to an enforced deviation from coplanarity in its competitive transition states. In this way stereoelectronic control[19] or the differences in allylic stabilization will be greater. Thus, strong evidence that resonance form **4c** contributes significantly to the anion stability is provided by the axial-equatorial rate ratio.[20] Furthermore, evidence against "ylide"-type stabilization as being of significance is provided by an examination of the reactivity of the quaternary iodide **5**. When **5** was heated for 45 h at 80 °C, then for another 24 h at 100 °C in *tert*-butyl alcohol-*O*-*d*-CD_3OD (1:4.1 ratio) containing CD_3ONa, 0.30 M, no exchange at any position was detectable.[23] At 35 °C in the same medium and at lower base concentration (0.22 M) the half-life for H_4 in **1** was 20 min.

Syn-Anti Selectivity. A comparison of the rates of exchange of H_2 vs. H_1 or H_4 vs. H_3 shows marked preference for syn exchange (10^3). Factors which might differ in their degree of stabilization of an anion as a function of this stereochemistry are (a) steric, (b) coulombic, and (c) cation effects. Since both steric and coulombic effects would be likely to stabilize the anion anti to the nitroso oxygen, some involvement of the cation seemed probable to account for preferential syn stabilization. Indeed, precedents have appeared in the literature where internal coordination in the cis anion of a propenyl ether was proposed to explain the preponderance of cis isomer formed by isomerization of allyl phenyl ether to the propenyl ether using potassium *tert*-butoxide.[24] We therefore sought to examine the role of the potassium ion in the exchange reaction of **1**. Since crown ethers are known to form stable complexes with potassium ion, the observation of a change in the rate of an H-D exchange reaction when crown ether is added provides strong evidence for the involvement of a potassium ion in the rate-determining step.[14] We have studied the effect of addition of a slight excess (vs. K^+) of dicyclohexyl-18-crown-6 on the rates of exchange of H_2 and H_3 in **1**. As the data in Table III show, the rate of exchange of H_3 at either 0.06 or 0.15 M concentration of base is unaffected by the addition of crown ether. The exchange of H_2 in the presence of excess crown ether does show a slight retardation, twofold at 0.06 M concentrations of base and fourfold at 0.15 M concentration of base. If the role of potassium ion were to be of importance in preferential exchange of a syn proton, a retardation comparable to the 10^3 rate ratio would be anticipated. The observation of only slight retardation in the rate of exchange of H_2 is a strong indication that the potassium ion is *not* contributing to the syn selectivity. One explanation which could account for the great difference in stabilities of syn vs. anti anions arises from a consideration of the symmetry properties of their molecular orbitals.[25] The π framework of the two anions can be visualized as being isoelectronic with butadiene dianion[26] (if the dipolar structure for the *N*-nitroso group is considered). The symmetry of the HOMO's of these two anions will be as depicted in Figure 2. A stabilizing interaction between the carbon and oxygen atoms is possible, which would be expected to be much greater in the syn anion. This explanation is qualitatively the sae as that theoretically derived by Epiotis[28] to account for the greater stability of many cis- over trans-disubstituted ethylenes in which the substituents are fluorine, chlorine, or alkoxy groups. Still earlier, a similar theoretical argument was expressed by Hoffmann and Olofson[29] to account for the reports by Bauld[30] of strong preferential formation of cis diacyloxyolefins from the metal reductions of diketones. If one considers diketones. If one considers that formation of a cis olefin is en- that formation of a cis olefin is energetically favored in spite of steric factors, it would not be unreasonable that the same influence of nonbonded attractive forces could lead to the still

Table III. Effects of Crown Ether (CE)[a] on Exchange Rates[b]

Run	Base, M	CE, M	Proton	$10^5 k_{obsd}$, s^{-1}	$10^5 k_{chem}$, s^{-1}	Rate ratio[c] H_2	Rate ratio[c] H_3
7	0.06	0.066	H_3	12.2 ± 2 (0.873)	3.7		
			H_2		35 ± 2 (0.988)[d]	0.37	0.6
8	0.06	0.0	H_3	14.9 ± 0.6 (0.993)	6.3		
			H_2		94 ± 7 (0.988)		
9	0.15	0.152	H_3	25.3 ± 1.5 (0.983)	17		
			H_2		54 ± 6 (0.940)	0.20	0.7
5	0.15	0.0	H_3	33.0 ± 1 (0.995)	24		
			H_2		264 ± 6 (0.999)		

[a] Dicyclohexyl-18-crown-6 was used. [b] Quoted as in Table II. [c] Ratio of rates of *tert*-butoxide-catalyzed exchange in presence and absence of crown ether. [d] The identical rate of exchange of H_2 occurred in the presence of 1.05 equiv of macroheterobicyclic diamine.[34]

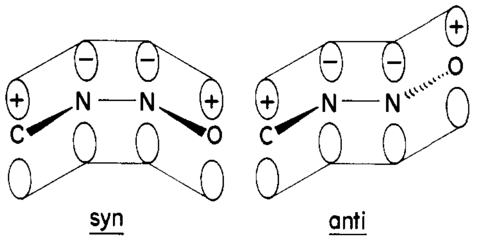

Figure 2. The symmetry of the HOMO of the anion $C^{-}N{=}NO^{-}$.

greater syn selectivity in **1**, since there will be no counterbalancing steric factors present. Very probably the high syn selectivity reported in the reduction of asymmetric oximes to aziridines using lithium aluminum hydride[31] is attributable to the same effects of orbital symmetry.

Such rationalizations are most certainly tentative at present and experiments to test their validity are currently in progress.

Experimental Section

All kinetic measurements were performed on a Varian HA-100 NMR spectrometer, equipped with an SD-100 deuterium spin decoupler. The probe temperature was maintained at 27 ± 0.5 °C throughout all kinetic runs. Dicyclohexyl-18-crown-6 obtained from Aldrich was used without further purification. *tert*-Butyl alcohol-*O*-*d* was prepared by the procedure of Cram and Nielsen.[32] The deuterium content was assayed by comparison of the OH signal's integral with that of the ^{13}C side band of the *tert*-butyl hydrogens. The alcohol contained 97.5% *d* and was stored in a serum-capped flask in a desiccator. Periodic checks on deuterium content showed no change. A stock solution of potassium *tert*-butoxide in *tert*-butyl alcohol-*O*-*d* was prepared by adding freshly cut potassium to the alcohol under an atmosphere of nitrogen. After heating until the metal had disappeared the resultant solution was stored in a serum-capped flask in a desiccator. Base concentration was measured by titration (HCl and phenolphthalein) and solutions of lower concentration were prepared by volumetric dilution.

Each kinetic run was carried out on 17 mg (0.067 mmol) of **1** dissolved in 0.4 ml of *tert*-butyl alcohol-*O*-*d* at 27 °C in a thin-walled 5-mm NMR tube. Upon the addition with vigorous shaking of 0.1 ml of *tert*-butyl alcohol-*O*-*d* containing the desired concentration of base, the tube was placed in the spectrometer for continuing integral measurements.

Kinetics. For the exchange reaction $SH + ROD \rightleftharpoons SD + ROH$ two errors may arise when the reaction is simply treated as a pseudo-first-order reaction. As shown previously by Streitweiser and coworkers,[33] the influence of the back reaction can be appreciable and is accounted for by employing x_e, the isotopic content of the solvent pool at the end of the reaction as the infinity value for the exchange. Since x_e changes during the exchange, the derived rate constant should be corrected by a factor of $2b/Q$. Since this factor is essentially the same for each proton, it has not been included in our determination of relative rates. Only the effect of solvent pool which determines both x_0 and x_e (the concentrations of isotope at beginning and end of the exchange of a proton) and has different values for each proton exchange process has been used in obtaining the rate constants. The values in each case were obtained by NMR measurement of the proton content of the solvent at the beginning and end of the reaction (i.e., OH vs. aromatic absorption).

The details of the preparation of compounds **1**,[13] **5**,[4] and **1** selectively deuterated at H_4[13] have appeared previously.

Acknowledgment. The authors thank the National Research Council of Canada for support of this work.

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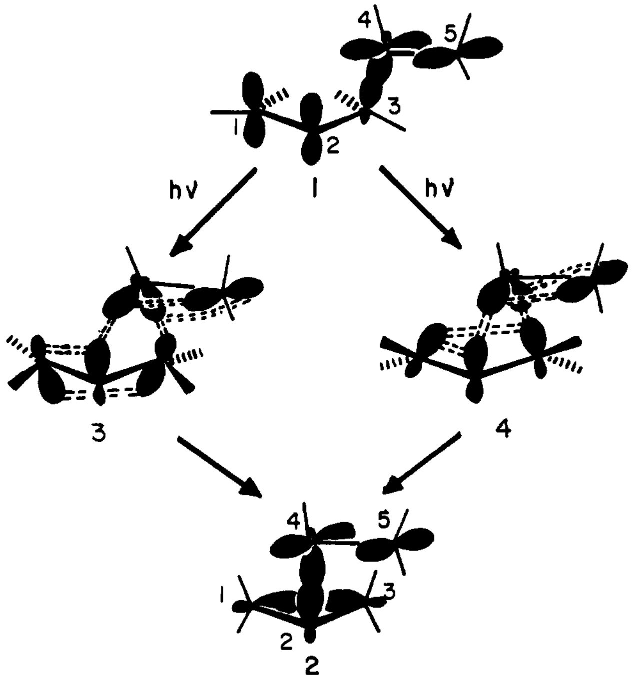
Stereochemical and Mechanistic Aspects of the Di-π-methane Rearrangement. Effect of Structural Constraints Which Preclude Preferred Modes

Patrick S. Mariano,* Richard B. Steitle, Darrel G. Watson, Michael J. Peters, and Elliott Bay

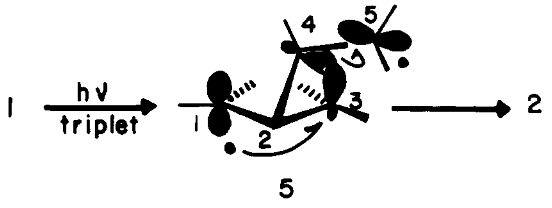
*Contribution from the Department of Chemistry, Texas A & M University,**
College Station, Texas 77843. *Received June 30, 1975*

Abstract: A study of stereochemical and mechanistic aspects of the di-π-methane rearrangement using 2-phenylspiro[5.5]undeca-1,7-diene (**6**) is reported. The sole product of direct irradiation of **6** is 11-phenyltricyclo[5.4.0.$0^{7,11}$]undec-2-ene (**7**). The spirodi-π-methane **6** was unreactive under triplet-sensitized irradiation conditions which employed both benzophenone and acetophenone. This inertness is due to an unreactive triplet-excited **6** rather than inefficient energy transfer from the triplet sensitizers, since **6** serves as an effective quencher of the well-known benzophenone–benzhydrol photoreduction to benzpinacol. The singlet and triplet photochemistry of **6** in comparison to that of the close structural analogue, 1-phenyl-3-methyl-3-(1-*cis*-propenyl)cyclohexene (**23**), is interpreted in terms of preferred di-π-methane reaction modes and how structure controls the relative energies of competing singlet and triplet reaction transition states.

Our recent studies[1] in the area of di-π-methane photochemistry have concentrated on stereochemical aspects of this quite general[2] excited-state conversion of 1,4-dienes (**1**) to vinylcyclopropanes (**2**). Results from our previous investigations[1] and those of Zimmerman and co-workers[3] have indicated that transformations of singlet-excited di-π-methanes follow concerted mechanisms and the configurational integrity at the centers of stereochemistry, i.e., the migrating C-4–C-5 π bond, C-3, and C-1, appear to be controlled by a remarkable energetic preference for transition states having what we have termed[1b] anti-disrotatory orbital geometries (**3**) over their syn-disrotatory (**4**) competitors. The existence and magnitude of this energetic preference seems to derive from factors other than orbital topology[4] or orbital symmetry,[6] since both transition states or concerted reaction pathways are predicted to be equally energetic or allowed on the basis of first-order orbital control methodologies.



Investigations of the stereochemistry of the triplet di-π-methane rearrangement are less abundant than of its singlet counterpart.[8] Thus, information from which to draw conclusions about mechanistic details and factors that control stereochemistry remain absent. In an early report,[1b] we presented mechanistic arguments to temporarily rationalize the stereospecificity of the triplet rearrangements.[9] Our conclusion was that triplet-reactive di-π-methanes reorganize to π-substituted cyclopropanes using a nonconcerted, two-step pathway via an intermediate cyclopropyldicarbinyl diradical (**5**), from



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