D/H Exchange in Nitro Diastereomers

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The two diastereomers of 4-nitro-1,3-diphenylpentan-1-one behave differently in deuterium for hydrogen exchange in DMSO-d_6/D_2O solutions using various bases as catalyst. Reaction of the erythro diastereomer gives largely the same diastereomer upon D/H exchange (retention), i.e., exchange exceeds epimerization. Pyridine and acetonitrile as solvents lead to faster epimerization than exchange. In the threo diastereomer (DMSO-d_6 solution), epimerization exceeds exchange, and the anion to some extent regains the same hydrogen originally removed by the base on the opposite face. 2-Bromo-4-nitro-1,3-diphenylbutan-1-one undergoes ring closure to the cyclopropane faster than exchange (within seconds). The cyclopropane shows faster exchange than equilibration, i.e., retention of configuration, although it is the hydrogen α to carbonyl that is involved.

The complexities of hydrogen transfer reactions in aqueous systems were first demonstrated by Eigen and co-workers.[1] Later work by Streitwieser and co-workers elucidated many facets of the acid−base chemistry of very weak acids[2] and helped to establish the scale of acidities that figure prominently in the discussion of hydrocarbon acidities in major textbooks.[2,3] Following earlier studies of Hogen-Esch and Smid,[4] Streitwieser and co-workers showed that contact ion pairs were prominent in cesium salts of carbanions whereas lithium salts were solvent-separated ion pairs, particularly in coordinating solvents.[5] The stereochemical aspects of hydrogen/deuterium exchange were extensively studied by Cram and co-workers.[6] In this work, a variety of stereochemical outcomes of the isotopic exchange reaction were elucidated, depending upon the system, base, and solvent, although retention of configuration was prominent in substrates such as sulfones.[7]

In ketones, early work by Wilson et al. showed that deuterium exchange, racemization of optically active substrates, and also bromination at the position α to the carbonyl group were equivalent in rate.[8,9] The results were explained in terms of long-lived, planar, resonance stabilized anions.[6] Nitroalkanes might have been expected to be similar, in view of their greater acidity (ca. 7 pK units greater than ketones).[3b] Presumably, the more stable nitronate anion should be longer-lived and more subject to symmetrical solvation and loss of stereochemical integrity.[10,11]

The nitro group is the source of unusual phenomena, e.g., its weak hydrogen-bonding ability (in aliphatic systems).[12,13] Nitromethane is not highly soluble in water, despite the fact that three of the four major atoms are polar and the oxygens have several unshared pairs of electrons.[14] The oxygens of the nitro group are not highly basic, despite a high negative charge density on the oxygens.[15]

Bordwell and co-workers contrasted the kinetics of base-catalyzed proton removal of nitroalkanes with the equilibrium constants for the dissociation of the nitroalkanes as acids ($R_2CHNO_2 > RCHNO_2 > CH_3NO_2$).[16] The kinetic order ($CH_3NO_2 > RCH_2NO_2 > R_2CHNO_2$) is the opposite of the equilibrium order of acidities. Our results

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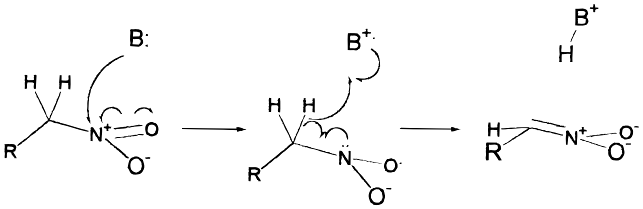
showed the same kinetic order for D/H exchange (R = methyl) in DMSO-d_6/D_2O.

In cases where the ammonium cation is in close proximity to the carbon of the anion from nitromethane, PM3 calculations indicate that the carbon of the nitronate is markedly nonplanar.[17] This may have stereochemical consequences for exchange reactions that involve contact ion pairs.[2,6,18] The bare nitronate anion, or the ion pair where the cation is located near the oxygens, is predicted to be planar. The nonplanarity of the nitronate persists through a "periodic box" reaction field calculation[19] in which the ion pair is surrounded by a reaction field of 216 water molecules (but only the ion pair is minimized in geometry). In a nonreaction field calculation, the ammonium and nitronate were separated first by two and then by four water molecules (2 × 2) in a full-minimization calculation. In the former case, a slight nonplanarity was still evident, but in the second case, the nitronate became effectively planar.

When base-catalyzed reactions of nitro compounds are considered, the possibility of an electron transfer reaction arises (e.g., eq 1).[20,21] The radical anions from nitromethane and from acetone are nonplanar, whereas the radical anion from dimethylsulfone resembles the original starting material. The nonplanarity renders the faces of the nitro group radical anion nonequivalent, a fact that could have stereochemical consequences. Gaussian RHF/6-311G+(d,p) calculations were used to provide the structures shown in Figure 1.[15]

Figure 1. Radical anion of acetone and of nitromethane, showing the nonplanarity of carbon and of nitrogen.



(1)

Little or no isotope effect for deuterium/hydrogen exchange would be expected if electron transfer is rate determining step in D/H exchange, whereas if hydrogen removal from the radical anion is rate limiting, a sizable isotope effect would be expected.[22] Bordwell and also Kresge and their respective co-workers found normal kinetic isotope effects for exchange of nitroalkanes (ca. 7), and in a few cases, high isotope effects were observed, which may be the result of tunneling.[23,24]

In D/H exchange reactions of the diastereomers of this study, no effect of 1,3-dinitrobenzene was seen using either triethylamine or DBU (**7**) as base.[25] In certain addition reactions, Hoz has shown that both one-electron and two-electron processes are possible. The reaction is initiated in the lowest energy route, but a crossover from the single-electron to the two-electron pathway may occur as the reaction manifolds cross one another.[26] In the present case, if the crossover occurs "early", 1,3-dinitrobenzene may be ineffective in intercepting the radical

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(15) (a) Ab initio RHF/6-31G* calculations predict a 0.45 negative charge on oxygen (using the Mulliken approximation). Gaussian 92, Revision E., Frisch, M. J.; Trucks, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Stewart, J. J. P.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1992. (b) Later calculations used Gaussian 94W, Revision D3, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Kieth, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1995.

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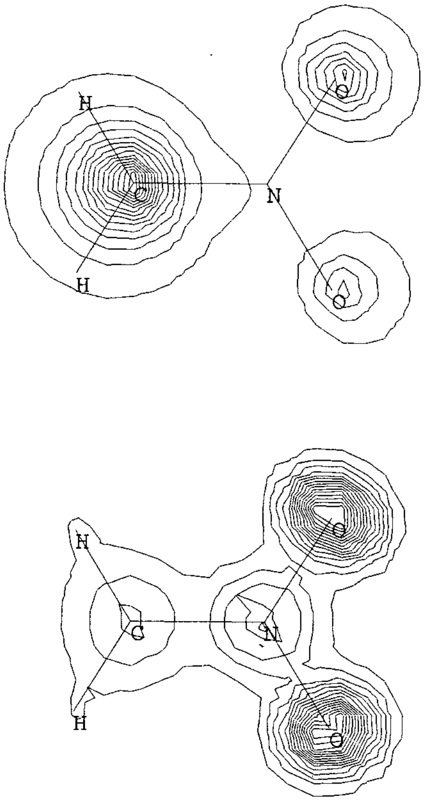
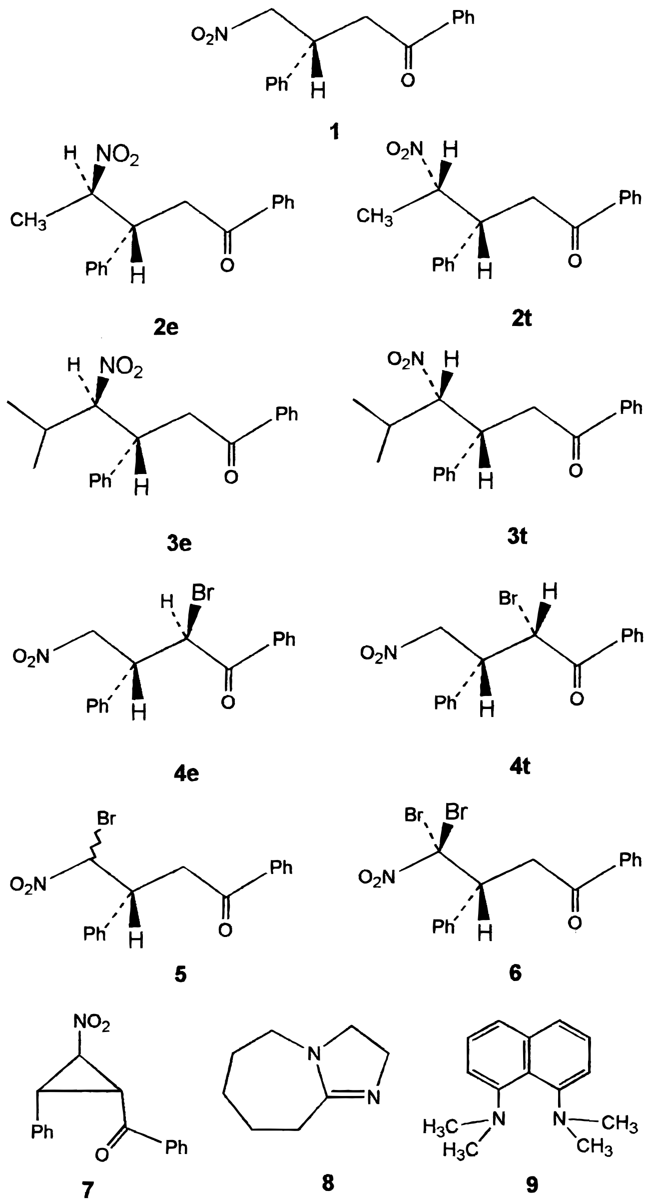


Figure 2. PME illustrations of the HOMO and of total electron density from occupied orbitals in nitromethane anion.

anion. It is difficult to envisage a one-electron addition to the nitro group vs a two-electron hydrogen removal by base as being close enough in reaction trajectory to permit crossover, however.

A complicating feature of nitronate anion chemistry is the lore that reprotonation of the anion will occur on oxygen, thus forming an acinitro structure.[27] Early chemists were able to isolate acinitro compounds.[27,28] Our attempts to isolate acinitro intermediates were not successful in the compounds of this study. As Figure 2 shows, the HOMO of the nitronate anion has a large coefficient on carbon, whereas the total charge density is higher on the oxygens. Thus, if the protonation reaction is HOMO/LUMO controlled, as may be the case with triethylammonium ion as proton donor, carbon should be the main center of reprotonation.[29] If the reaction is charge controlled, as perhaps with H^+ in the Nef reaction, oxygen should be protonated.[30] Modeling of the interaction of ammonium ion with the anion from nitromethane by PM3 calculations (very low dielectric constant medium) showed that the ammonium ion migrated from the face of the anion to the edge, near the oxygens. This is the result of the overwhelming influence of electrostatics. No proton transfer to oxygen was observed. Thus, the proton transfer must be associated with an appreciable barrier. In a reaction field of 200 water molecules, the ammonium ion maintained its location over the face of the anion and transferred a proton to carbon. However, under the reaction conditions, some protonation on oxygen, followed by reionization and subsequent protonation on carbon, cannot be ruled out. The stereochemical arguments given below would still apply.

Scheme 1



D/H Exchange in Nitro Diastereomers

The exchange reactions were studied in the diastereomers of structure **1**–**3**, in the brominated compounds, i.e., **4**–**6**, and in the cyclopropyl system **7** (Scheme 1).[31] The bromine derivatives **4**–**5** permit exploration of another facet of the chemistry of carbanions, i.e., ring closure vs exchange and equilibration. The study of diastereomeric systems affords certain advantages over study of enantiomers. The deuterium vs hydrogen ratio

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Table 1. Exchange vs Epimerization of *erythro*-4-Nitro-1,3-diphenylpentan-1-one, 2e

run	solvent	base	rate effects	description	product ratio[a] **2e:2t**	isoracemization[b]
1	DMSO/D_2O (10:1) (w/w)	NEt_3	$k_{ex} > k_{ep}$	retention	1.5:1	low
2	DMSO/*t*-BuOD (7.2:1)	NEt_3	$k_{ex} \approx k_{ep}$		0.8:1	high
3	$CDCl_3$/*t*-BuOD	NEt_3	$k_{ex} \ll k_{ep}$	inversion	0.12:1	high
4	CD_3OD	NEt_3	$k_{ex} \approx k_{ep}$		1:1	
5	DMSO/D_2O (10:1)	Proton Sponge	$k_{ex} > k_{ep}$	retention	1.4:1	med
6	DMSO/D_2O (10:1)	DBU	$k_{ex} > k_{ep}$	retention	ca. 1.5:1	*c*
7	DMSO/D_2O (10:1)	NaCN	$k_{ex} > k_{ep}$	retention	1.9:1	med
8	DMSO/D_2O (10:1)	NaOAc	$k_{ex} > k_{ep}$	retention	2.1:1	low
9	CD_3OD	NaCN	$k_{ex} > k_{ep}$	retention	ca. 2:1	
10	Pyr-d_5/D_2O (10:1)	NEt_3	$k_{ex} \ll k_{ep}$	inversion	0.17:1	trace
11	CD_3CN/D_2O (10:1)	NEt_3	$k_{ex} < k_{ep}$	inversion	0.56:1	med
12	DMSO/D_2O (15:1) (0 °C)	NEt_3	$k_{ex} > k_{ep}$	retention	1.4:1	med

[a] Evaluated as closely as possible at one half-life of the fastest reaction process, commonly k_{ex}. The "product ratio" is the quantity of **2e** *with deuterium* vs the total quantity of **2t** formed. [b] Low signifies less than 25%, med 25–50%, and high >50%, evaluated at less than 30% of the fastest reaction process, usually k_{ex}. Commonly, the evaluation was done at ca. 15% reaction. The difficulty is due to secondary exchange of the isoracemized product, i.e., it is like "hitting a moving target". [c] Difficult to evaluate.

Table 2. Exchange vs Epimerization of *threo*-4-Nitro-1,3-diphenylpentan-1-one, 2t

run	solvent	base	rate effects	description	product ratio[a] **2e:2t**	isoracemization[b]
1	DMSO/D_2O (10:1) (w/w)	NEt_3	$k_{ex} < k_{ep}$	inversion	3.5:1	trace
2	DMSO/*t*-BuOD (7.5:1)	NEt_3	$k_{ex} < k_{ep}$	inversion	ca. 2.3:1	high
3	$CDCl_3$/*t*-BuOD (18:1)	NEt_3	$k_{ex} < k_{ep}$		0.72:1	high
4	DMSO/D_2O (14:1)	Proton Sponge	$k_{ex} < k_{ep}$	inversion	3.5:1	*c*
5	DMSO/D_2O (14:1)	DBU	$k_{ex} < k_{ep}$	inversion	ca. 2.9:1	
6	DMSO/D_2O (11:1)	NaCN	$k_{ex} < k_{ep}$	inversion	ca. 4.6:1	*c*
7	DMSO/D_2O (10:1)	NaOAc	$k_{ex} < k_{ep}$	inversion	4.1:1	med
8	CD_3OD	NaCN	$k_{ex} < k_{ep}$	inversion	6.3:1	trace
9	Pyr-d_5/D_2O (12:1)	NEt_3	$k_{ex} < k_{ep}$	inversion	1.5:1	trace
10	CD_3CN/D_2O (8.6:1)	NEt_3	$k_{ex} < k_{ep}$	inversion	1.7:1	med

[a] Evaluated as closely as possible at 1 half-life of the fastest reaction process, commonly k_{ep}. [b] Low signifies less than 25%, med 25–50%, and high >50%, evaluated at less than 30% of the fastest reaction process, commonly k_{ep}. Usually the evaluation was done at ca. 15% reaction. [c] Difficult to evaluate.

in the original diastereomer as well as in the epimeric product are easily seen without the necessity of a difficult re-resolution of enantiomers.[32]

Similar concentrations of the two diastereomers of **2** were observed upon equilibration proceeding from either starting material (e.g., 49% **2t** and 51% **2e** in pyridine-d_5:D_2O as solvent). Thus, differences in the stability of the diastereomers should not be a major factor in these reactions.[10]

The ratio of the rates of exchange of hydrogens α to nitro vs hydrogens α to carbonyl decrease in the order: **1** > **2** > **3**, i.e., a steric order. In **1**, the diastereotopic hydrogens α to nitro exchange more rapidly, but at somewhat different rates (roughly 2:1 using NEt_3 as catalyst). The substrate is conformationally mixed and it is not easy to tell which diastereotopic hydrogen is the one that exchanges the most rapidly.[33] In **3**, the hydrogens α to carbonyl exchange much more rapidly than hydrogens α to nitro. Thus, the 7 orders of magnitude greater intrinsic acidity of hydrogens α to nitro is easily overcome by steric factors.

Methyl Diastereomers 2. Tables 1 and 2 list the exchange vs epimerization data for the erythro isomer **2e** and for the threo isomer **2t**, respectively. Table 1 shows that a variety of stereochemical results are found for **2e**, depending upon solvent, co-solvent, and base. In run 1, with triethylamine as base, the NMR doublet for the α methyl group at δ 1.2 for **2e** changes to a singlet much faster than the methyl signal at δ 1.5 appears for the epimer, **2t**. The change from a doublet methyl to a singlet indicates exchange, i.e., the $CH_3C\mathbf{H}NO_2$ is replaced by $CH_3C\mathbf{D}NO_2$. Figure 3 shows a point later in the reaction, where the original isomer **2e** has almost completely exchanged, whereas the epimer **2t** is present at a much lower level. Since the rate of isotopic exchange of **2e** exceeds the rate of epimerization to **2t**, $k_{ex} > k_{ep}$, the stereochemical result may be termed "retention of configuration" using an adaptation of the definitions suggested by Cram.[6] Accompanying the "retention" pathway are generalized reaction path(s) leading to randomization.

Runs 1–3 show the effect of moving to progressively less polar solvent with a "less-available" deuterium source. In runs 2 and 3, with *tert*-butyl alcohol-d_{10} as deuterium source, epimerization catches up and then exceeds exchange. To a certain extent, the anion intermediate regains hydrogen (instead of one of the large excess of deuteriums in the solvent) on the opposite face. Cram termed such behavior "isoracemization".[32,34] Isoracemization is prominent in the more viscous solvents, especially where *tert*-butyl alcohol-d_{10} is the deuterium source. Comparison of runs 1 and 12 (a low-temperature run), shows that stereochemistry is about the same ("retention"), but isoracemization is more prominent at low temperatures. In run 4, with the nonviscous CD_3-

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(32) Cram, D. J.; Roitman, J. N. *J. Am. Chem. Soc.* **1971**, *93*, 2235.

(33) Ground state conformation is, of course, irrelevant, but it does aid in identification of the reactive hydrogen. (a) Curtin, D. Y. *Rec. Chem. Progr.* **1954**, *15*, 111. (b) Hammett, L. P. *Physical Organic Chemistry*; McGraw-Hill: New York, 1970; p 119, terms the principle the "Curtin Principle".

(34) (a) Cram, D. J., ref 6, pp 87, 98, 103. (b) Cram, D. J.; Willey, F.; Fischer, H. P.; Scott, D. A. *J. Am. Chem. Soc.* **1964**, *86*, 5510. (c) Cram, D. J.; Gosser, L. *J. Am. Chem. Soc.* **1964**, *86*, 2950.

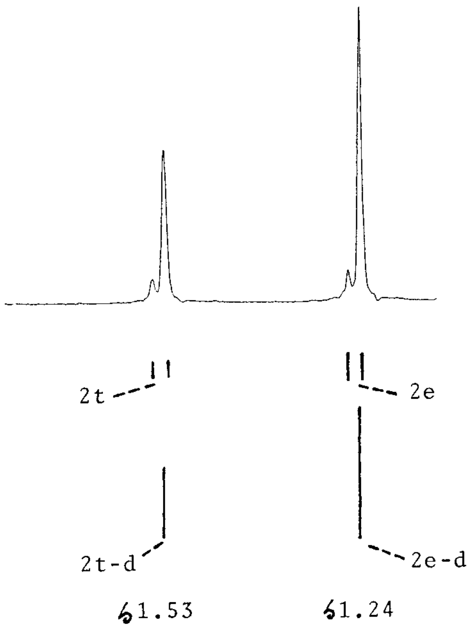


Figure 3. Methyl NMR signals from the exchange/epimerization of **2e** in DMSO-d_6/D_2O after ca. 39 h, showing almost complete exchange, but much less epimerization to form **2t**. The doublets represent unexchanged substrate, whereas the singlets indicate that exchange has occurred.

OD as solvent, isoracemization disappears and the stereochemistry is random.

The effect of base is seen in runs 1, 5, 6, 7, and 8. Despite the variety of bases used, the stereochemical result is predominant retention. DBU (**8**), a strong base, gave an extremely fast reaction, whereas the sterically hindered base, Proton Sponge (**9**, Aldrich), gave a very slow reaction. One possible explanation for the lack of effect of base on stereochemistry is that deuterium delivery occurs through a solvent separated ion pair. Thus, differential steric effects for various protonated bases for deuterium donation have little effect on stereochemistry. The base originally used by Wilson in work on D/H exchange in ketones was sodium acetate.[8] Acetate as base operating on **2e** was moderately reactive, although cyanide was much more so, as predicted from their relative pK_b's.[3] Retention again predominates.

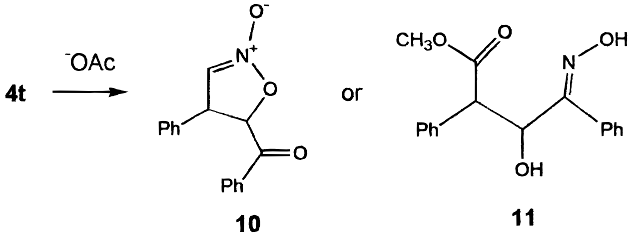
The basic solvents, pyridine-d_5 and CD_3CN showed faster epimerization than D/H exchange of the original isomer, **2e**. It was as if the nitronate intermediate largely picked up deuterium if it went to the epimer but regained hydrogen if the original diastereomer was reformed.

Threo Diastereomer 2t. As Table 2 shows, epimerization of **2t** to form **2e** occurred more rapidly than D/H exchange in the original isomer under almost all conditions studied, i.e., $k_{ep} > k_{ex}$. The epimer **2e** that had appeared after about a half-life showed ca. 65% deuterium present, and the original isomer **2t** retained about 70% hydrogen. Again this "inversion" route was as if the intermediate anion largely gained deuterium when it formed the epimer, but regained hydrogen to form the original diastereomer. The reaction "overshoots" the 1:1 equilibrium mixture of products, forming a temporary excess of **2e**.[34]

Isopropyl Compounds 3. The reaction of α-isopropyl compound was somewhat difficult to follow. Surprisingly, at equilibrium, the ratio of diastereomers was roughly unity. With NEt_3, exchange α to nitro was exceedingly slow, and decomposition was evident if higher temperatures were used. With cyanide as base (DMSO-d_6/D_2O solution at ambient temperature), a reasonably rapid reaction ensued; for **3e**, exchange exceeded epimerization, and some isoracemization was noted. For **3t** with cyanide as base, epimerization is slightly faster than exchange, and the reaction again "overshoots" the equilibrium mixture of products.

Bromo Compounds 4. Treatment of the α-bromo compound, **4e**, with triethylamine in DMSO-d_6/D_2O gave extremely rapid ring closure to the cyclopropane.[35-37] This reaction was complete, with starting material **4e** no longer observable, before the first NMR spectrum could be determined, ca. 1.5 min. Only a single hydrogen is lost from the bromo compound **4e**, and thus the cyclopropane **7tt** is formed with a complete complement of three ring hydrogens. Thus, k_c, ring closure from an anion intermediate, is faster than exchange either α to nitro or α to carbonyl. Ring closure, k_c, in **4e** is faster than exchange in the nonbrominated compound **1** (half-life for exchange ca. 3 min using similar concentrations) during which **4e** would have reacted many half-lives. Thereafter, the cyclopropane **7tt** exchanged surprisingly slowly in view of the activation afforded by the high s-character C−H bonds of the three-membered ring. The subsequent reactions are the same as for **7tt** prepared independently and subjected to the reaction conditions.

The isomeric α-bromo compound **4t** also undergoes reaction extremely rapidly to form a different compound, which thereafter forms other products. Kohler and, later, Smith isolated an intermediate from this reaction, whose structure was initially considered to be the **10** but later revised to **11**[35,36] (eq 2). We can neither confirm nor deny these structures, except to note that only an AB NMR splitting pattern at δ **4**−**5** was seen for the intermediate of our spectra (not an ABX). Too little of **4t** was available to study the reactions in detail.



eq. 2

With the γ-bromo compound (**5**), quite different results were found. Ring closure was again quite fast (complete within minutes), but now complete exchange α to nitro had also occurred. The same cyclopropane **7tt** as from **4e** is formed, but now with two ring hydrogens and a deuterium. A second compound, believed to be **7ct** (cf. Scheme 2), is also evident. The dibromide **6**, upon addition of NEt_3, gave broad, nondescript NMR signals

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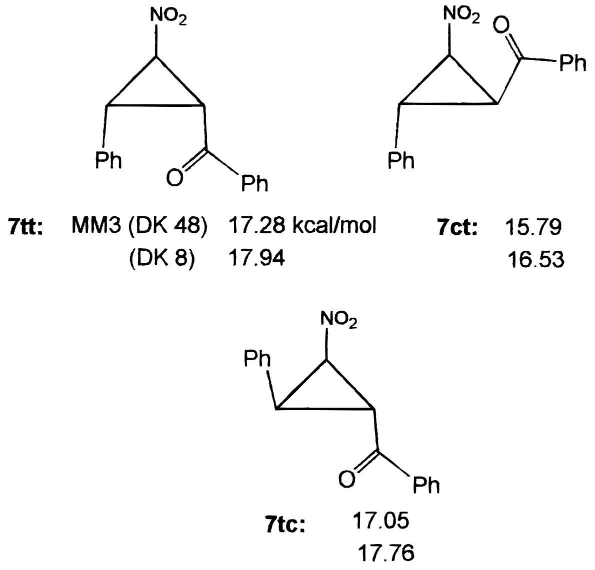
(35) Kohler, E. P.; Smith, L. I. *J. Am. Chem. Soc.* **1922**, *44*, 624.

(36) (a) Smith, L. I.; Davis, B. K. *J. Am. Chem. Soc.* **1954**, *76*, 5376. (b) Smith, L. I.; Holly, E. D. *J. Am. Chem. Soc.* **1956**, *78*, 1472. (c) Smith, L. I.; Rogier, E. R. *J. Am. Chem. Soc.* **1951**, *73*, 3831; 3837. (d) Smith, L. I.; Engelhardt, V. *J. Am. Chem. Soc.* **1949**, 71, 2671; 2676.

(37) (a) Neurieter, N. P.; Bordwell, F. G. *J. Am. Chem. Soc.* **1963**, *85*, 1209. (b) Kende, A. S. *Organic Reactions*, **1960**, *11*, 261. (c) Breslow, R.; Posner, J.; Krebs, A. *J. Am. Chem. Soc.* **1963**, *85*, 234.

Scheme 2



indicative of the presence of free radicals. It was not investigated further.

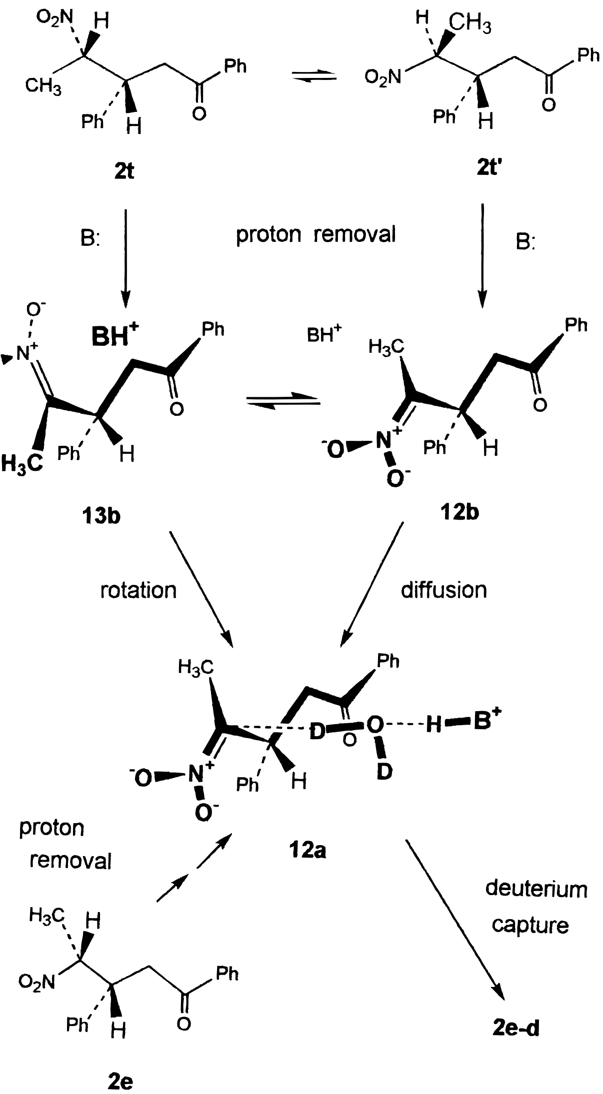
With the principal isomer of the cyclopropanes available in quantity (**7tt**), the more rapid exchange occurred α to carbonyl, not α to nitro. This may be a simple steric effect. With this cyclopropane, $k_{ex} \gg k_{ep}$ for both acidic hydrogens.[38]

Four isomers of **7** are possible, of which the all-cis isomer is the least stable. Of the remaining three isomers, molecular mechanics predicts **7ct** to be the most stable. The equilibration and reactions of related cyclopropanes were extensively studied by Smith and coworkers, who were able to obtain three of the possible four isomers in a slightly different system.[35-37] In our hands, **7tt** was persistent under equilibrating conditions, although decomposition hampered determination of an equilibrium ratio.

Discussion

In most nonbasic solvents, diastereomer **2e** rapidly exchanges D for H, but retains the **2e** configuration. Diastereomer **2t** rapidly forms **2e** under the same conditions. In many cases with **2t**, the reaction overshoots the 1:1 ratio of diastereomers found at equilibrium giving a temporary preponderance of **2e**. Thus, a stereoselective kinetic process favoring **2e** from either starting material seems to exist for which a common intermediate may be sought.[9k] Structures **12** and **13** show the two low-energy conformations for the nitronate anion found under a variety of calculations. Of these two, **12** seems to be the more stable.[39,40] The interconversion of **12** and **13** appears to have relatively low energy requirements. Via the highest possible point, the barrier to internal rotation (where nitro passes phenyl) lies about 3 kcal above the minimum energy structure. At the lowest energy passage, the barrier to internal rotation is only about 1.7 kcal.

Scheme 3



Scheme 3 illustrates exchange vs epimerization processes. Solvent-separated ion pairs are shown in Scheme 3, in which the ammonium ion serves as a general acid by furnishing a hydrogen or deuterium to D_2O, which could then deliver a deuterium to **12a**. The dielectric constant of the medium ($DMSO/D_2O$) is greater than 48,[41] which is high enough so that the electrostatic attraction favoring contact ion pairing should be attenuated. Modeling by PM3 indicates that hydrogen ion delivery from ammonium ion to the nitronate $CH_2{=}NO_2^-$ via one and even two intervening water molecules is remarkably efficient if the molecules are properly aligned. However, if any one of the molecules is slightly misaligned, other processes occur, but seldom hydrogen ion delivery to the nitronate, i.e., entropy takes its toll. From the modeling studies, one can appreciate the effect of organized

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(38) Walborsky, H. M.; Youssef, A. A.; Motes, J. M. *J. Am. Chem. Soc.* **1962**, *84*, 2465.

(39) A PM3 calculation in a periodic box of several hundred water molecules on a non-ion-paired molecule was considered to be the most reliable, giving an energy difference of 3 kcal. Ion-paired molecules give the same order of stability, but the energy difference is accentuated.

(40) (a) A PM3 calculation gave a substantial energy preference for *si* vs *re* approach of ammonium ion to **12** (i.e., to form **12a** and not **12b**) in a reaction field of several hundred water molecules. The energy difference varied from calculation to calculation, but **12a** was consistently favored. Only the nitronate **12** was minimized in energy, as otherwise reaction would have occurred thus merely providing the energy of the substrate. In full minimizations, ammonium ion seemed to become "hung up" over aromatic groups, as in **12b**, cf.: Dougherty, D. A. *Science* **1996**, *125*, 163. (b) Na, J.; Houk, K. N.; Hilvert, D. *J. Am. Chem. Soc.* **1996**, *118*, 6462 and related papers.

(41) Okamoto, Y. *Adv. Phys. Org. Chem.* **1995**, *30*, 173.

systems (e.g., enzymes) as opposed to random systems.[42] The modeling studies point up the acidifying effect of the cation on H_2O, as in the absence of the cation, water by itself does not furnish a proton to nitronate.[43]

Beginning with **2e**, proton removal by base is believed to give the intermediate **12a**. Since BH^+ lies in a relatively unhindered location, deuterium for hydrogen exchange occurs readily, giving BD^+. Reprotonation, either directly by BD^+ or by deuterium oxide in a solvent-separated ion pair, occurs from the same (less hindered) face of the nitronate, thus forming **2e-*d*** (deuterium present).

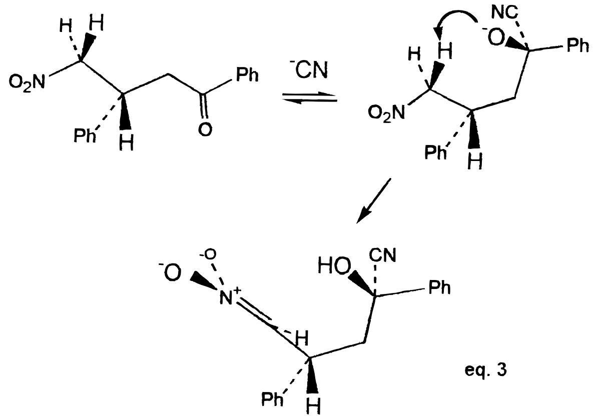
In the case of **2t**, deprotonation is believed to give either **12b** or **13b**.[39] In order to form the least hindered intermediate possible (**12a**), either diffusion of $BH(D)^+$ to the opposite side of **12** or else internal rotation of the $CH_3C{=}NO_2^-$ group of **13b** must occur. Once present, **12a** would could capture a deuterium to give **2e-*d***. Modeling of **13b** by PM3 in a periodic box of water molecules shows that diffusion is faster than internal rotation. However, diffusion is less efficient in specifically forming the important intermediate **12a**.

One point of interest is the identity of the deuterium donor. The ammonium ion, acetic acid, or HCN are the most acidic substances present, being some 5−10 orders of magnitude more acidic than water. Although these "acids" should be more reactive than D_2O, the similarity of the stereochemical data shown in Tables 1 and 2 suggest that a common agent furnishes the deuterium.

The data of Tables 1 and 2 indicate that isoracemization is reasonably prominent in solutions of high viscosity or where a sterically hindered deuterium donor, *tert*-butyl alcohol-d_{10}, is present. In other solutions, e.g., DMSO-d_6/D_2O, isoracemization also occurs, to a small extent. In highly hydrogen bonded DMSO solutions, mechanisms such as Cram's "conducted tour", are less likely as competition between the nitronate and the solvent occurs to hydrogen bond to BH^+.[6] In the conducted tour mechanism, the base removes hydrogen from the substrate but remains in contact with the anion thus formed via various contact points and eventually finds its way to the opposite face of the molecule, where return occurs.[6] Amine bases figured prominently in cases where Cram and co-workers found isoracemization.[6] Modeling experiments indicate that HCN or ammonium ion is remarkably persistent in the vicinity of the nitronate **12** or **13** (in a partially vacated field of water molecules), but a strict hydrogen bonding geometry is not maintained.

The very rapid ring closure processes of **4** raise interesting questions. The bromine α to carbonyl probably does not activate the hydrogen γ to carbonyl a great deal. Why then should ring closure of **4e** be more rapid than exchange of **4e** or exchange of the unbrominated compound **1**? The explanation that comes to mind is internal return slows the exchange rate of **1**. Yet, Kresge and Powell concluded that every act of ionization results in exchange, in reactions of *p*-nitrophenylnitromethane-α-*t* with amine bases in toluene as solvent, i.e., no internal return occurs.[24] It is surprising that internal return does not occur from the initially formed ion pair in this low dielectric constant medium, in view of the fact that the ultimate reaction in which the anion is reprotonated must involve a somewhat similar species. Modeling certainly shows that the return of hydrogen from a moderately strong acid (the ammonium ion) to a moderately strong base (the nitronate) takes place easily in a contact or solvent separated ion pair. Isoracemization is simply return of the hydrogen carrier to the opposite face of the nitronate, which does occur under certain conditions (cf. Tables 1 and 2).

Another question is whether the nitrogen bases, acetate, or cyanide are the primary agents that remove the proton α to nitro. Another possibility would be nucleophilic addition to carbonyl, followed by α hydrogen removal by the resulting oxide via a six-membered transition state (cf. eq 3). Modeling of the reaction of the tetrahedral intermediate resulting from NEt_3 addition or cyanide addition to carbonyl showed little tendency for subsequent oxide removal of the α hydrogen. It is difficult to achieve a linear transition state. In contrast, modeling indicates that direct proton removal by cyanide occurs easily.[44]



eq. 3

Over the years, several mechanisms have been cited to account for the retention of configuration observed in the D/H exchange of various substrates, e.g., sulfones.[45] Cram emphasized the importance of ion pairs and the solvation of the cation as an important element to "lead in" the deuterium source toward the original face of the substrate.[6,7] The modeling experiments of this study suggest some new facets, i.e., the tendency for planar anions to assume nonplanar character, if ion paired, and the acidification of the deuterium oxide by the cation in the solvent-separated ion pair.

The sensitivity of the reaction rate to the nature of the base (half-lives ranging from seconds to weeks) suggests that the base directly removes the hydrogen from the substrate. Steric hindrance is important in the interaction of substrate with bases, e.g., Proton Sponge, leading to slow reaction. On the other hand, the sensitivity of the stereochemistry of deuterium capture by the nitro-

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[42] (a) Kirby, A. J. *Acc. Chem. Res.* **1997**, *30*, 290−296. (b) Dugas, H. *Bioorganic Chemistry*, 2nd ed.; Springer-Verlag: Berlin, 1989; Chapter 1.

[43] (a) The argument is related to the well-known hydrolysis of water in solutions of di- or tervalent ions, resulting in an increase of pH of the solution. Prof. Ronald Breslow quoted a value of 7 p*K* units as the acidifying effect zinc on surrounding water molecules, Breslow, R. *Acc. Chem. Res.* **1996**, *28*, 146−153. (b) Breslow, R.; Conners, R. *J. Am. Chem. Soc.* **1996**, *118*, 6323−6324.

[44] According to A. J. Kirby,[42] "...intramolecular proton transfer reactions are generally inefficient".

[45] (a) Goering, H. L.; Towns, D. L.; Dittmer, B. *J. Org. Chem.* **1962**, *27*, 736. (b) Corey, E. J.; Kaiser, E. T. *J. Am. Chem. Soc.* **1961**, *83*, 490. (c) Corey, E. J.; Konig, H.; Lowry, T. H. *Tetrahedron. Lett.* **1962**, 515. (c) Our simulations did not show an inordinately high barrier to conformational change, as predicted by Corey and co-workers,[45b,c] although pronounced conformational preferences were found.[18a]

nate to the structure of BD^+ is not large. This suggests that deuterium donation via a relay effect through a solvent-separated ion pair is involved and that BD^+ may not necessarily be a direct deuterium donor.

Experimental Part

4-Nitro-1,3-diphenylbutan-1-one (1). This material was prepared by the method of Kohler, mp 95−97 °C (lit.[31a] mp 103 °C). The ^{1}H NMR spectrum was simulated and solved by LAOCON[45] (iterative rms error 0.01): $CDCl_3$ δ 3.37 (dd, 1H, $J = -17.7$, 7.6 Hz, H_2), 3.41 (dd, 1H, $J = -17.7$, 6.2 Hz, $H_{2'}$), 4.16 (m, 1H, H_3), 4.63 (dd, 1H, $J = -12.5$, 8.0 Hz, H_4), 4.77 (dd, 1H, $J = -12.5$, 6.6 Hz, $H_{4'}$), 7.2−8.0 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 39.5, 41.7, 79.8, 127.6−139.3, 196.7.

4-Nitro-1,3-diphenylpentan-1-ones (2). These were prepared by literature methods. In our hands, they were separated by fractional crystallization by the triangle scheme using ethanol as solvent; **2t**, mp 98−99 °C (lit.[31a] mp 100 °C), as cubes; **2e**, mp 69−70 °C (lit.[31a] mp 72 °C), as needles. Configuration was elucidated by determining the steric energies using MM3 for a series of points up to 30° on either side of the minimum energy conformation for each of the three main conformations (using the dihedral driver option). The dihedral angles between vicinal hydrogens at C3 and C4 at each point were also taken from MM3 calculations. Using the program LACA,[46] the NMR coupling constants were calculated by the Altona procedure[47] at each point, and using the steric energies as Boltzmann weighting factors, the conformation contributions to the overall ^3J were found; summation provided a predicted ^3J. For the high-melting isomer eventually assigned as **2t**, ^3J as calculated was 7.5 Hz; observed $^3J = 6.2$ Hz. The spectrum was solved by LAOCON successive simulations until the calculated spectrum was superimposable on the observed spectrum. For the high-melting isomer: ^{1}H NMR ($CDCl_3$) δ 1.53 (d, 3H, $J = 6.6$ Hz, CH_3), 3.45 (dd, 1H, $J = -17.7$, 7.2 Hz, H_2), 3.61 (dd, 1H, $J = -17.7$, 6.5 Hz, $H_{2'}$), 3.96 (m, 1H, H_3), 4.99 (dq, 1H, $J = 6.6$, 6.2 Hz, H_4), 7.2−7.9 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$) δ 17.0, 40.1, 44.8, 86.4, 127.9, 128.1, 128.3, 128.8, 133.5, 136.7, 138.4, 197.2. For the low-melting isomer, eventually assigned at **2e**, the calculated ^3J was 10.5 Hz; the observed ^3J is 9.8 Hz; simulated spectrum: ^{1}H NMR ($CDCl_3$) δ 1.36 (d, 3H, $J = 6.6$ Hz, CH_3), 3.26 (dd, 1H, $J = -17.1$, 4.4 Hz, H_2), 3.54 (dd, 1H, $J = -17.1$, 9.6 Hz, H_2), 3.94 (m, 1H, H_3), 4.90 (dq, 1H, $J = 6.6$, 9.8 Hz, H_4), 7.1−7.9 (m, 10H, Ph). The methyl resonance occurred at δ 1.2 in DMSO-d_6 solutions. ^{13}C NMR ($CDCl_3$) δ 18.1, 41.6, 45.7, 87.5, 128.0−138.7, 196.7.

5-Methyl-4-nitro-1,3-diphenylhexan-1-ones (3e and 3t). This compound was prepared by condensation of 2-methyl-1-nitropropane with 1,3-diphenyl-2-propen-1-one using the method of Kohler for **2e** and **2t**. The condensation reaction afforded a large preponderance of one diastereomer. The dominant isomer, subsequently assigned as **3t**, mp 146.0−147.5 °C as fine needles. The ^{1}H NMR spectrum was simulated: ^{1}H NMR ($CDCl_3$) δ 1.02 (d, 3H, $J = 6.6$ Hz, CH_3), 1.19 (d, 3H, $J = 6.6$ Hz, CH_3), 2.21 (m, 1H, H_5), 3.39 (dd, $J = -17.6$, 7.1 Hz, $H_{2'}$), 3.49, (dd, $J = -17.6$, 6.4 Hz, $H_{2'}$), 4.13 (1H, apparent quartet, $J = 6.4$, 7.4 Hz, H_3), 4.78 (1H, apparent triplet, $J = 7.4$ Hz, $H_{4'}$), 7.2−8.0 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ 17.8, 19.9, 29.0, 41.1, 41.2, 97.2, 127.9, 128.2, 128.6, 128.7, 128.9, 129.2, 133.6, 136.9, 138.7, 197.4; MS (HREI) parent ion (311.1521) not found, 264.1519 ($M^+ - HNO_2$), 8.9% (σ 1.79), 145.1020 ($C_{11}H_{13}$), 15.0% (1.56), 105.0346 (C_7H_5O), 100.0% (5.56); MS (FAB, Na) m/z 334 (M + Na = 334). The best material for the minor isomer obtained (assigned as **3e**) showed a mp of 110.2−111.4 °C as fine needles. ^{1}H NMR ($CDCl_3$) δ 0.98 (d, 6H, $J = 6.6$ Hz, CH_3), 1.87 (m, 1H, $J = 5.2$, 6.6 Hz, $H_{5'}$), 3.17 (dd, $J = -16.1$, 2.5 Hz, H_2), 3.58, (dd, $J = -16.1$, 7.9 Hz, $H_{2'}$), 4.07 (1H, m, $J = 2.5$, 7.9, 9.7 Hz, H_3), 4.68 (1H, dd, $J = 9.7$, 5.2 Hz, $H_{4'}$), 7.2−8.0 (m, 10H, Ph); MS (HREI) parent ion 311 not found, 264.1524 ($M^+ -$ HNO2) 8.2% (σ 3.64), 145.1024 ($C_{11}H_{13}$), 14.4%, (4.3), 105.0703 (C_7H_5O) 100.0% (−1.21); MS (FAB, Na) 334 (M^+ + Na = 334). Application of a abbreviated procedure similar to LACA indicated that the threo isomer should have $J_{34} \approx 7$ Hz (as is observed for the major product) whereas the erythro isomer is predicted to have $J_{34} \approx 9$ Hz, close to the values found in the NMR spectra as simulated by LAOCON.

2-Bromo-4-nitro-1,3-diphenylbutan-1-ones (4e and 4t). These materials were prepared by the method of Kohler, **4t**, mp 125−126 °C (lit.[35−37] mp 129 °C) as fine needles, and **4e**, mp 97−98 °C (lit.[35−37] mp 100 °C, revised from earlier values) as fine needles. In general, these bromides showed a variety of melting points in samples that were quite pure by NMR. A mp of 108−110 °C was more common. The configuration of the high-melting isomer, **4t**, was assigned using the LACA procedure; predicted: $^3J_{23} = 7.9$ Hz (observed $^3J_{23} = 7.5$ Hz). The ^{1}H NMR spectrum of **4t** was simulated ($CDCl_3$) giving final values with rms error of 0.013: δ 4.30 (m, 1H, $J = 7.5$, 8.8, 3.6 Hz, H_3), 5.02 (dd, 1H, $J = -13.4$, 3.6 Hz, H_4), 5.25 (dd, 1H, $J = -13.4$, 8.8 Hz, $H_{4'}$), 5.65 (d, 1H, $J = 7.5$ Hz, H_2), 7.2−8.0 (m, 10H, Ph). The ^{1}H NMR spectrum of the low-melting isomer, **4e**, was simulated, with a rms error of 0.081 ($CDCl_3$): δ 4.47 (m, 1H, $J = 9.6$, 4.3, 9.4 Hz, H_3), 5.02 (dd, 1H, $J = -13.3$, 9.6 Hz, H_4), 5.33 (dd, 1H, $J = -13.3$, 4.3 Hz, $H_{4'}$), 5.63 (d, 1H, $J = 9.4$ Hz, H_2), 7.2−8.0 (m, 10H, Ph). The use of LACA gave a predicted $J_{23} = 9.7$ Hz (observed 9.4 Hz); ^{13}C NMR ($CDCl_3$) δ 45.6, 47.2, 79.2, 128.3, 128.9, 129.1, 129.5, 134.3, 134.4, 191.1.

Danger: Although neither E. P. Kohler nor Lee Irvin Smith[36] reported the slightest problem in this preparation, the writer experienced an extreme skin irritation from the bromination reaction of **1** to form **4e** and **4t**. This necessitated the closure of the laboratory for some months to all but minor uses. The allergic response was characterized initially by an itching and burning of facial skin, especially the eyelids. The victim should resist the human urge to rub the eyelids at all costs. No amount of washing the hands, using soap and water, acetone, ammonia or dilute acid removed the traces of chemical from the hands in a satisfactory manner, and each time the face was touched, a new wave of inflammation was initiated. At the worst point, the facial skin started to slough off, producing a condition resembling the aftermath of a moderate sunburn. The worst of the allergic response lasted about four months, but persists to the present, in part. Operations as simple as weighing out a few milligrams sample of **4** now (some years later) produce a new inflammation. The offending chemical may have been a side product, because once purified, **4** caused less discomfort. Compounds **5** and **6**, on the other hand, had no deleterious effect.

4-Bromo-4-nitro-1,3-diphenylbutan-1-one (5) and 4,4-Dibromo-4-nitro-1,3-diphenylbutan-1-one (6). These materials were synthesized by the method of Kohler (in our hands, in very low yield), **5**: mp 105−107 °C (lit.[31a] mp 93 or 90 °C (reported as two separate compounds)); ^{1}H NMR ($CDCl_3$) δ 3.59 (m, 2H, H_2 and H_2), 4.33 (m, 1H, H_3), 6.46 (d, 1H, $J = 6.6$ Hz, H_4), 7.3−8.0 (m, 10H, Ph). A second isomer was visible in preparative scale reactions, but could not be isolated, $J_{3,4} = 8.4$ Hz.

Compound **6** was the major product of any base catalyzed bromination of **1**, mp 157.0−158.5 °C (lit.[31e] mp 144−146 °C). The ABX ^{1}H NMR ($CDCl_3$) spectrum was solved explicitly: δ 3.72 (dd, 1H, $J = -17.6$, 2.6 Hz, H_2), 4.01 (dd, 1H, $J = -17.6$, 10.0 Hz, H_2), 4.95 (dd, 1H, $J = 2.6$, 10.0 Hz, H_3), 7.2−8.0 (m, 10H, Ph); ^{13}C ($CDCl_3$) δ 42.2, 55.2, 128.5−133.9, 194.8.

1-Benzoyl-2-nitro-3-phenyl cyclopropanes (7). Compound **7tt** was prepared by the method of Kohler and Engelbrecht,[47] mp 98.8−100.2 °C (lit.[47] 98 °C), as fine needles, or in another modification, as rather large prisms: ^{1}H NMR ($CDCl_3$) δ 3.85 (dd, 1H, $J = 4.8$, 11.4 Hz, C**H**Ph), 4.09 (dd, 1H, $J = 3.7$,

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(46) Bothner-By, A. A. *Adv. Magn. Reson.* **1965**, *1*, 115. The LAOCN-5 PC version (QCMP049) from Quantum Chemistry Program Exchange, Indiana University, Bloomington, IN, adapted (and improved) by K. J. Tupper from QCP458, of L. Cassidei, and O. Sciacovelli, Univ. of Bari, Bari, Italy. LAOCON4 was also occasionally used.

(47) Stanley, J.; Matallana, A.; Kingsbury, C. A. *J. Phys.-Org. Chem.* **1990**, *3*, 419−427.

(48) Haasnoot, C. A. G.; deLeeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

11.4 Hz, C**H**COPh), 5.44 (dd, 1H, $J = 3.7$, 4.8 Hz, C**H**NO$_2$), 7.1−8.2 (m, 10H, aromatic); ^{13}C NMR (CDCl$_3$) δ 36.7, 37.5, 63.2, 128.0−136.5, 190.5. A second material, believed to be **7ct**, was isolated in minuscule yield, mp 86−88 °C (lit.[47] mp 88 °C), as "puff-balls": ^{1}H NMR (CDCl$_3$) δ 3.44 (dd, 1H, $J =$ 7.7, 8.9 Hz, C*H*Ph), 4.34 (dd, 1H, $J = 7.7$, 3.4 Hz, C*H*COPh), 5.05 (dd, 1H, $J = 3.4$, 8.9 Hz, C*H*NO$_2$), 7.1−8.1 (m, 10H, aromatic). There was no indication of the third cyclopropane, mp 142 °C, reported by Kohler et al.[47]

Procedure for NMR Determinations. Approximately 15 mg of the substrate (say **2**), was weighed out and mixed with approximately 0.6 mL of DMSO-d_6 (ACROS) plus 0.6 mL of deuterium oxide (Aldrich) and placed in a dried NMR tube using dried Pasteur pipets. The deuterated solvents all appeared pure by NMR, and no attempts were made to further purify them by distillation. To start the run, the base, e.g., redistilled triethylamine, was added. The concentration of the base was determined by integration. The initial concentrations, typically, were **2**, 0.088 M, and triethylamine, 0.03−0.1 M. Due to the speed of the reaction, no more than a trace of DBU was used as base (concentrations typically ca. 0.006 M). The concentration of Proton Sponge, as base, was ca. 0.03 M. With cyanide, the concentration was ca. 0.02 M or less due to the speed of the reaction. Sodium acetate was used at ca. 0.2 M. The reactions were followed by ^{1}H NMR using approximately eight spectra over 2 half-lives (a smaller number for extremely fast reactions). The half-lives varied from a few minutes (DBU catalyst), to eight hours (NEt$_3$), to weeks (Proton Sponge), and months (reactions run in CDCl$_3$/*tert*-butyl alcohol-d_{10}). COSY spectra were run to determine which peaks were associated with one another. The instruments used extended from a Varian VXR 200, a GE Nicolet 360, and finally to a GE Omega-300 instrument.

Calculations. PM3 calculations were done with the HyperChem software. In view of the tendency of this software to give different results in different calculation runs, a strong effort was made to achieve consistent data. MM3 calculations (1989 version) were run on a VAX computer. Ab initio calculations were run with the Gaussian software[15] on a Pentium. On rare occasions, a Silicon Graphics IRIS system was used with the SPARTAN software.

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