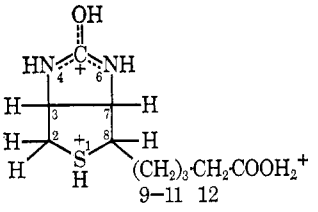
Table III. Pmr Chemical Shifts for D-Biotin[a] and Its Triprotonated Form

Solvent	C_2	C_8	C_3C_7	$C_9C_{10}C_{11}$	C_{12}	$CO_2H_2^+$	OH	NH
FSO_3H-SbF_5-SO_2	4.0–4.5		5.60	1.7–2.6	3.29	12.28 12.54	9.64	7.04 7.21
CF_3COOH[11]	3.10	3.47	4.81	1.73	2.62	...		...

[a] Chemical shifts in FSO_3H-SbF_5-SO_2 solution are given in parts per million from external TMS. Shifts in CF_3COOH are referred to internal TMS as standard.



XVIII

Relatively strong interactions between the sulfur atom in D-biotin and the protein to which it is attached have been suggested.[21,23] The fact that protonation of the sulfur occurs *trans* to the valeric acid side chain suggests that binding of the sulfur with the protein should occur from the same direction.[24] Attack from this side of the thiolane ring is particularly favorable in D-biotin in which the valeric acid side chain is *cis* to the ring junction. In L-biotin, any interaction with the sulfur would have to occur with approach from either the same side as the side chain or the same side as the ureido ring. Both of these modes of attack would be less favorable, on steric grounds, than in D-biotin, and indeed L-biotin shows no physiological activity.[28]

(23) A. C. Mildvan and M. C. Scrutton, *Biochemistry*, **6**, 2978 (1967).

(24) The steric requirements of the proton in such cases is a question that has not been completely resolved. In the protonation of ketones[25] and cyclic ethers[26] protonation from the least hindered side is always found, and our results accord with the view that in a conformational rivalry between the proton and nonbonding electrons, the final equilibrium position is primarily determined by the interaction properties of the proton.[27]

(25) G. A. Olah, M. Calin, and D. H. O'Brien, *J. Amer. Chem. Soc.*, **89**, 3586 (1967).

(26) G. A. Olah, P. J. Szilagyi, and J. Sommer, to be published.

(27) Footnote 17 in ref 17a.

Experimental Section

1,1-Dimethylurea was prepared from nitrourea and dimethylamine. Methylisourea *p*-toluenesulfonate was prepared from urea and methyl *p*-toluenesulfonate. Other urea and guanidine bases used were commercially available and, where necessary, were recrystallized before use.

Solutions of the bases in fluorosulfuric acid–antimony pentafluoride–sulfur dioxide were prepared as described earlier.[3] Proton spectra were obtained using a Varian Associates Model HA-100 spectrometer with a capillary tube of TMS as the internal lock signal. Chemical shifts, referred to this standard, were obtained using a frequency counter. Temperature measurements were made by means of a thermometer constructed to fit into a 5-mm nmr tube and are considered accurate to within ±1°.

^{15}N spectra were obtained by the indor method using the apparatus described previously.[3] The reference used for determination of ^{15}N shifts was a saturated aqueous solution of $^{15}NH_4NO_3$ for which ν_H/ν_N was found to be 9.8686442.

Rotational rates were computed at coalescence using the relationship

$$k = 1/\tau = \pi\left(\frac{\Delta\nu^2}{2}\right)^{1/2}$$

where $\Delta\nu$ is the chemical shift separation in hertz in the absence o exchange.

Acknowledgment. This work was possible through a grant of the National Institutes of Health. Hoffman LaRoche, Inc., is thanked for a gift of D-biotin.

(28) P. Gyorgy, *Vitamins*, **1**, 527 (1954).

The Stereochemistry of Protonation. XI

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Abstract: The stereochemistry of ketonization of exocyclic cyclohexane enols and tautomerism of *aci*-nitro compounds was reinvestigated. The enol of 1-acetyl-4-phenylcyclohexane was found to afford predominantly the less stable *cis* isomer on ketonization. Similarly, 1-*aci*-nitro-4-phenylcyclohexane tautomerized preferentially to *cis*-1-nitro-4-phenylcyclohexane when large proton donors were used. With smaller donors, the *trans* isomer was preferred. It was concluded that substituents at carbon 2 are not necessary for kinetic control leading to the less stable stereoisomer. The relationship of ground-state conformations to the transition states utilized is presently discussed. It is concluded, in keeping with our earlier postulate concerning kinetic control of ketonization, that approach of the proton donor in the least hindered way is usually the most important factor.

Some years ago, when the difference between kinetic and thermodynamic control of reactions was just becoming clear, we noted that many organic reactions involved unstable enol intermediates and that stereochemical preferences observed in these reactions are controlled by the kinetics of ketonization. Our hypothesis, which seems to be generally accepted, was that in many cases the less stable stereoisomeric product

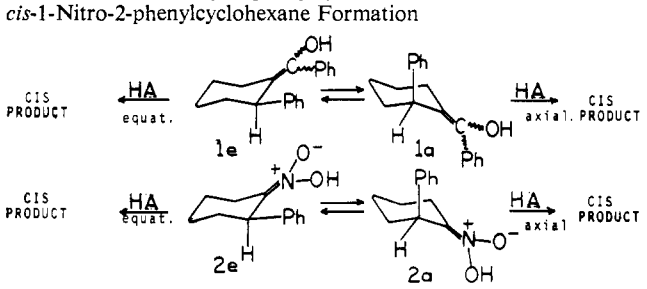
results from a kinetically controlled ketonization in which proton attack occurred from the less hindered direction.[1]

The cases initially discussed[1] and subsequently investigated[2] included exocyclic six- and five-ring enols, endocyclic five-ring enols, and less common examples. Only a few of the molecules considered were six-ring enols containing a bulky substituent at C-2.

Recently, Malhotra and Johnson[3a] suggested that our views on ketonization of 2-substituted exocyclic six-ring enols must be abandoned. The purpose of this report is to clarify the picture, put it in the proper perspective, and provide some recent results.

The enols **1** of 1-benzoyl-2-phenylcyclohexane and the *aci*-nitro tautomer **2** of 1-nitro-2-phenylcyclohexane were postulated by Malhotra and Johnson to exist in 2-phenyl axial conformations **1a** and **2a** due to $A^{(1,3)}$ strain.[3b] The predominance of *cis* product[1,2e] was rationalized with our hypothesis of less hindered attack, in this case axial, of the proton donor on conformations **1a** and **2a**[4] (see Chart I). Thus the Malhotra–Johnson

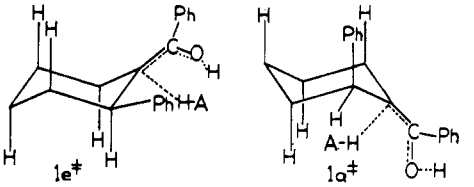
Chart I. *cis*-1-Benzoyl-2-phenylcyclohexane and *cis*-1-Nitro-2-phenylcyclohexane Formation



mechanism consists of application of our basic theory of less hindered approach to a different ground-state conformation.

More important, however, are the transition states in proceeding from enol or *aci*-nitro tautomer to product. Provided that the activation energy for the ketonization reaction is large compared with the barrier to conformational inversion, the proportion of conformations reacting is not necessarily related to the population of the ground-state conformations; instead, the stereochemistry utilized depends on the relative transition-state energies.[8] In the transition state[9] (note Chart II)

Chart II. Potential Transition States for the Ketonization of the Enol of 1-Benzoyl-2-phenylcyclohexane



two opposing factors must be considered. Transition state $\mathbf{1e}^{\ddagger}$ is formally derived from ground-state conformation **1e** while transition state $\mathbf{1a}^{\ddagger}$ is formally related to ground-state conformation **1a**. However, either transition state may arise independent of ground-state population.

Nevertheless, the transition-state energies will reflect the intramolecular van der Waals repulsions present in the related ground-state conformer and still present in the transition state. Additionally, the transition-state energies will be affected by proton donor–substrate (enol or *aci*-nitro compound) repulsions. In transition state $\mathbf{1a}^{\ddagger}$ $A^{(1,3)}$ strain is relieved, but 1,3-diaxial phenyl–hydrogen interactions along with 3,5-diaxial hindrance to proton approach are encountered. While transition state $\mathbf{1e}^{\ddagger}$ does suffer from $A^{(1,3)}$ strain, interactions due to an axial-phenyl substituent and hindrance to proton approach (in this case equatorial) are drastically decreased. Without knowledge of which effect, intramolecular or intermolecular repulsive forces, is dominant, it is not possible and seems unwise to select one of two[9] possibilities.

As a consequence of the uncertain conformation involved in the special case of 2-phenyl-substituted exocyclic cyclohexane enols, it seemed worthwhile to investigate 4-phenyl-substituted systems in order to ascertain the extent to which the same stereochemistry of protonation is followed when $A^{(1,3)}$ strain cannot be involved. For this study the 1-acetyl-4-phenylcyclohexane and 1-nitro-4-phenylcyclohexane systems were selected, since these could be compared with the 2-phenyl analogs previously investigated.[2a,e,10]

Synthetic Aspects and Configuration Assignments

The hitherto unknown *cis*- and *trans*-1-acetyl-4-phenylcyclohexanes (**3** and **4**) and *cis*- and *trans*-1-nitro-4-phenylcyclohexanes (**5** and **6**) were needed to establish configurations and as precursors to the enolic tautomers.

The synthesis of *cis*- and *trans*-1-acetyl-4-phenylcyclohexanes is delineated in the Experimental Section. Our configurational assignments of these ketones derive from sodium ethoxide equilibration which afforded an 11.5:1 ratio of *trans* to *cis* isomer. Also, bromination of the ketone stereoisomer **3** (*i.e.*, *cis*) in acetic acid occurred more rapidly (*vide infra*) than bromination of stereoisomer **4**, as expected for the less stable *cis* isomer.[2a,c]

The synthesis of *cis*- and *trans*-1-nitro-4-phenylcyclohexanes (**5** and **6**) is outlined in the Experimental Section. The configurational assignments of **5** and **6** are based on sodium bicarbonate equilibration. Starting with either **5** or **6** a predominance (81.0%) of the more stable *trans* isomer **6** resulted. Additionally, in the

(1) H. E. Zimmerman *J. Org. Chem.* **20**, 549 (1955).

(2) (a) H. E. Zimmerman, *J. Am. Chem. Soc.*, **78**, 1168 (1956); (b) H. E. Zimmerman and H. J. Giallombardo, *ibid.*, **78**, 6259 (1956); (c) H. E. Zimmerman, *ibid.*, **79**, 6554 (1957); (d) H. E. Zimmerman and T. W. Cutshall, *ibid.*, **80**, 2803 (1958); (e) H. E. Zimmerman and T. A. Nevins, *ibid.*, **79**, 6559 (1957); (f) H. E. Zimmerman and T. W. Cutshall, *ibid.*, **81**, 4305 (1959); (g) H. E. Zimmerman and A. Mais, *ibid.*, **81**, 3644 (1959); (h) H. E. Zimmerman and W. H. Chang, *ibid.*, **81**, 3634 (1959).

(3) (a) S. K. Malhotra and F. Johnson, *ibid.*, **87**, 5493 (1965); (b) F. Johnson and S. K. Malhotra, *ibid.*, **87**, 5492 (1965).

(4) The assignment of ground-state conformations of the *aci*-nitro compound **2** and the acetates of enol **1** was based on the half-band widths of the C-2 methine which in AX_2Y_2 systems is *ca.* 22 cps for axial and *ca.* 7 cps for equatorial hydrogens.[5] The validity of application of these values to AXY systems, where a first estimate[6,7] would predict half these values, needs further support.

(5) R. U. Lemieux, *et al.*, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(6) N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., New York, N. Y., 1964, p 80.

(7) E. W. Garbisch, *J. Org. Chem.*, **27**, 4249 (1962).

(8) D. Y. Curtin, *Record Chem. Progr.*, **15**, 111 (1954).

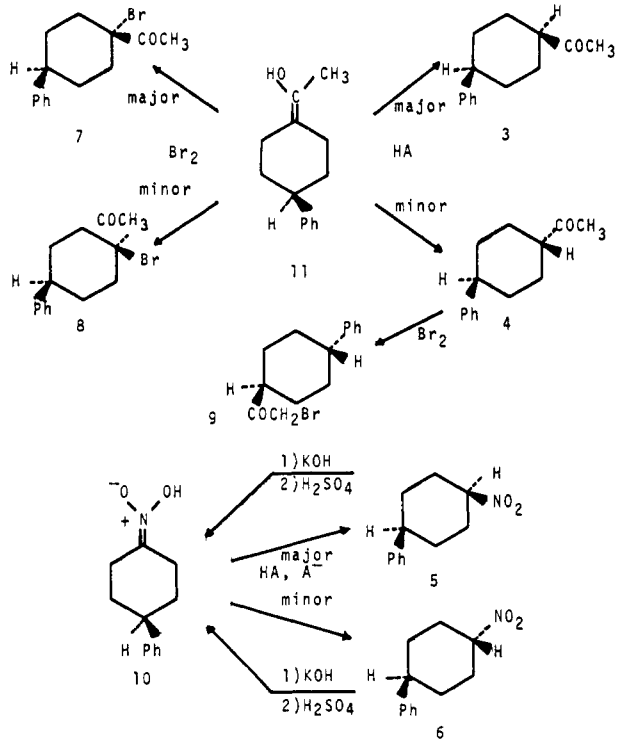
(9) Twist-boat conformations should be higher in energy than axial-phenyl conformations. Additionally, models suggest that twist-boat conformations should not give the observed selectivity. But, since the selectivity is small when considered in energy terms, these conformations cannot be excluded.

(10) The behavior of 4-phenylcyclohexanecarboxylic acid enol *vs.* the 2-phenyl isomer[2b,d,f] suggests that the less stable isomer is formed in both cases. This isolated case needed further support.

nmr spectrum of nitro isomer **5** the methine proton α to the nitro gave rise to a peak at τ 5.43 with a half-band width of 7 cps while the corresponding methine proton resonance in isomer **6** appeared at τ 5.70 with a half-band width of 26 cps. This, according to the general rule of half-band widths for AX_2Y_2 systems and relative positions of equatorial *vs.* axial hydrogens,[5] gives further support for our assignment of *cis* stereochemistry (equatorial methine proton) to **5** and *trans* (axial methine) to **6**.

Since reverse halogenation of α-bromo ketones has been shown[1,2a] to be a convenient method for generating unstable enol intermediates, we next directed our efforts toward the synthesis of the isomeric 1-acetyl-1-bromo-4-phenylcyclohexanes (**7** and **8**). These bromo ketones were obtained (note Chart III) by the reaction of *cis*

Chart III. Stereochemical Transformations of the Stereoisomeric 1-Acetyl-4-phenylcyclohexanes and 1-Nitro-4-phenylcyclohexanes



ketone **3** with bromine in acetic acid. The structure of the bromo ketones was demonstrated by debromination experiments (*vide infra*) with hydriodic acid and with zinc which yielded, in both cases, a mixture of ketones **3** and **4**. Only if the bromine atom were at C-1 or C-4 would a mixture of isomers be obtained. Facile debromination with dilute hydriodic acid is characteristic of α-bromo ketones. Additionally, nmr spectra of **7** and **8** showed that they were methyl ketones: τ 7.59, 3 H singlet, and 7.62, 3 H singlet, respectively.

Interestingly, bromination of *trans* ketone **4** using the same conditions as above proceeded more slowly and yielded several products, none of which were the desired bromo ketones. One of the major components was identified as 1-bromoacetyl-4-phenylcyclohexane (**9**) (see Chart III).

Also, 1-*aci*-nitro-4-phenylcyclohexane was required. Using the method of Zimmerman and Nevins,[2e] acidification of an ethanolic solution of the conjugate base of either **5** or **6** at −10°, we prepared 1-*aci*-nitro-4-phenylcyclohexane (**10**), mp 81.0–83.0°. The structural assignment was supported by the infrared spectrum which exhibited O—H stretching at 2.8–4.5 μ and C=N stretching at 6.01 μ, and by the nmr spectrum which showed aromatic (5 H), cyclohexyl (9 H), and enolic (1 H at τ −1.25) protons. Further evidence for the structure was found in the tautomerization studies (*vide infra*) giving rise to the 1-nitro-4-phenylcyclohexane stereoisomers.

Results

Proton Transfer Stereochemistry. Debromination of the 1-bromo-1-acetyl-4-phenylcyclohexanes (**7** and **8**) was accomplished using zinc and various proton donors, following the general method described by us earlier.[2c,11] The results are summarized in Table I and Chart III.

Table I. Ketonization of the Enol of 1-Acetyl-4-phenylcyclohexane

Starting bromo ketone	Debrominating agent	Solvent	Proton source	% *cis* isomer
8	Zinc	Methanol	Collidine·HCl	62.4
8	Zinc	Methanol	Ammonium chloride	60.5
8	Zinc	Acetonitrile	Collidine·HCl	76.6
7	Zinc	Methanol	Ammonium chloride	64.6
7	Zinc	Acetonitrile	Collidine·HCl	78.8

Tautomerization of the *aci*-nitro compound **10** was effected using several buffer solutions. The distributions of *cis*- and *trans*-1-nitro-4-phenylcyclohexane stereoisomers formed in these experiments are collected in Table II and Chart III.

Table II. Tautomerization of 1-*aci*-Nitro-4-phenylcyclohexane

I[a]	Buffer solutions	% *cis* isomer
6	LiOAc–HOAc	37.3
6	Collidine–collidine·HCl	60.5
6	2-Methylquinoline–2-methylquinoline·HCl	61.3
6	Pyridine–pyridine·HCl	52.9
5	LiOAc–HOAc	38.4

[a] Precursor to *aci*-nitro compound **10** tautomerized.

Conclusions

The results summarized in Tables I and II clearly show that ketonization of the enol of 1-acetyl-4-phenylcyclohexane (**11**) and tautomerization of 1-*aci*-nitro-4-phenylcyclohexane (**10**) proceed with moderate and varying selectivity to form the corresponding *cis* isomers **3** and **5** predominantly. As found in our earlier efforts,[2a-f] use of larger proton donors leads to increased selectivity favoring the *cis* isomers. The view expressed earlier by us[1] that the 3,5-axial hydrogens blocking axial approach by a proton donor leads to a preferred equatorial attack (note Figure 1) is still valid, since, as noted above, in the present examples there is no substituent at C-2 to be taken into account.

(11) Attempts at using hydriodic acid in acetone to effect a reverse bromination, successfully utilized with 1-bromo-1-acetyl-2-phenylcyclohexane stereoisomers,[2e] were not fruitful due to rapid equilibration of the product 1-acetyl-4-phenylcyclohexane stereoisomers under the reaction conditions.

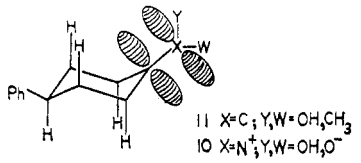


Figure 1. 1-*aci*-Nitro-4-phenylcyclohexane and enol of 1-acetyl-4-phenylcyclohexane.

There seems to be somewhat greater selectivity in the enol ketonization than in the *aci*-nitro tautomerization. For example, we observed a predominance of *trans*-1-nitro-4-phenylcyclohexane (**6**) when tautomerization was carried out using acetic acid as the proton source[12] as compared to a predominance of *cis* isomer **5** when using larger proton donors. Thus, with small proton donors product thermodynamics may become the major factor reflected in the *aci*-nitro- to nitrocyclohexane transition-state energies; tautomerization can then form the product of more hindered attack.[13,14]

Other examples of ketonization and tautomerization of exocyclic cyclohexane enols and *aci*-nitro compounds not containing bulky substituents at C-2, occurring by way of a kinetically controlled proton attack from the less hindered equatorial direction, are available in the literature and substantiate our findings.[15,16]

Thus, in applying our general hypothesis of less hindered approach in the special case of 2-substituted cyclohexane enols and *aci*-nitro compounds, Malhotra and Johnson have differed from us only in their selection of the conformation used. However, independent of assignment of ground-state conformations, transition-state conformations are controlling, and evidence which is available demonstrates that a preferred exo (*i.e.*, equatorial) approach often dominates. In any event, our general theory is substantiated as noted even by Johnson and Malhotra.[3a]

Experimental Section[17]

***cis*- and *trans*-1-Nitro-4-phenylcyclohexanes.**[18] To a mildly refluxing solution of 57.00 g (0.30 mol) of 4-phenylcyclohexanone oxime,[19] 6.00 g of urea, and 357.00 g (2.04 mol) of dibasic sodium phosphate in 600 ml of acetonitrile was added dropwise with stirring a solution of 45.60 g (0.60 mol) of peracetic acid (112.50 g of a 40% solution in acetic acid, Becco, containing 1% sulfuric acid) in 200 ml of acetonitrile. The addition was complete in 1 hr, and the reaction mixture was stirred an additional 2.5 hr at reflux. After cooling to room temperature, the organic layer was decanted from the precipitated salts and diluted with *ca.* 500 ml of ether. The ether solution was extracted with water, 5% sodium hydroxide, and water, dried, and concentrated *in vacuo* leaving 43.32 g of a yellow oil which was chromatographed on a 5 × 80 cm silica gel (Davison grade 950, 60–200 mesh) column slurry packed with hexane. Elution was with 4 l. of 3% ether–hexane, 6 l. of 5% ether–hexane, and 6 l. of 30% ether–hexane; 500-ml fractions were collected. Fractions 9–20 gave 9.528 g of a yellow crystallizing oil which by fractional recrystallization from hexane yielded 5.345 g, mp 58–62°, of impure *trans*-1-nitro-4-phenylcyclohexane. Fractions 21–37 afforded 30.961 g of a yellow solid, mp 69–74°, which was shown by infrared and nmr to be 4-phenylcyclohexanone.

The mother liquors from the above fractional recrystallization were chromatographed on a 2.5 × 100 cm silica gel (Davison grade 950, 60–200 mesh) column slurry packed in hexane. Elution was with 9 l. of 2% ether–hexane; 40-ml fractions were collected. Fractions 60–100 contained 2.769 g of a white solid, characterized as *trans*-1-nitro-4-phenylcyclohexane, and was combined with the impure material of the same identity obtained above. Recrystallization of the combined material from hexane gave 4.500 g (7.4%), mp 63.5–64.5°, of pure *trans* isomer. Physical data were the following: infrared (CS_2) 3.23, 3.26, 3.30, 3.48, 6.97, 7.02, 7.28, 7.41, 8.64, 9.74, 10.00, 10.08, 10.85, 11.20, 11.60, 12.20, 13.30, 14.35 μ; nmr ($CDCl_3$) τ 2.75 singlet (5 H, aromatic), 5.70 six-line multiplet (1 H, W_H = 26 cps, axial $CHNO_2$), 7.12–8.93 multiplet (9 H, cyclohexyl).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.21; H, 7.38; N, 6.82. Found: C, 69.99; H, 7.62; N, 6.63.

Fractions 111–210 contained 2.543 g of a semisolid. Recrystallization from pentane yielded 0.458 g (0.7%), mp 62.0–63.5°, of *cis*-1-nitro-4-phenylcyclohexane. Physical data of this compound were the following: infrared (CS_2) 3.23, 3.26, 3.30, 3.40, 3.48, 7.24, 7.45, 7.70, 8.91, 9.43, 9.94, 10.00, 10.99, 11.12, 12.60, 13.30, and 14.35 μ; nmr ($CDCl_3$) τ 2.80 singlet (5 H, aromatic), 5.43 multiplet (1 H, W_H = 7 cps, equatorial $CHNO_2$), 7.04–8.58 multiplet (9 H, cyclohexyl).

Anal. Calcd for $C_{12}H_{12}NO_2$: C, 70.21; H, 7.38; N, 6.82. Found: C, 70.09; H, 7.48; N, 6.98.

Quantitative Infrared Analysis of Mixtures of *cis*- and *trans*-1-Nitro-4-phenylcyclohexanes. The same general technique described earlier[2a] was used, utilizing the relation $R = QF$, where R is the ratio of *cis*- to *trans*-nitro isomers in a given mixture. $Q = (D'D_t'' - D''D_t')/(D''D_c' - D'D_c'')$. D', D_t, and D_c are optical densities of a given mixture, of pure *trans* isomer, and of pure *cis* isomer, respectively, and the superscripts refer to the analytical wavelengths: λ' 12.20 μ, and λ'' 12.60 μ. F was determined empirically from three known mixtures as shown in Table III and was found to have an average value of 1.031. All spectra were run on a Perkin-Elmer 421 spectrophotometer at a total concentration of 40 mg/0.15 ml of CS_2. The calibration runs indicate an estimated accuracy of ±1.0% *cis* isomer due to infrared uncertainties.

Table III. Infrared Analysis of Mixtures of *cis*- and *trans*-1-Nitro-4-phenylcyclohexanes

Actual % *cis* isomer	D' (12.20 μ)	D'' (12.60 μ)	Q (calcd)	R (act.)	F (calcd)	Calcd % *cis* isomer
100.0	0.796	0.103	...	...	...	...
75.0	0.600	0.195	2.919	3.00	1.028	75.1
50.0	0.456	0.318	0.932	1.00	1.073	49.0
25.0	0.258	0.374	0.336	0.33	0.993	25.7
0.0	0.042	0.486	...	...	...	...

1-*aci*-Nitro-4-phenylcyclohexane.[20] To 10.0 ml of 20% ethanolic potassium hydroxide was added 0.700 g (3.71 mmol) of *trans*-1-nitro-4-phenylcyclohexane and the resulting solution stirred under nitrogen for 3.0 hr; 20 ml of water was added and the clear solution cooled to −10°. A sulfuric acid–ethanol solution (1:3) was added with stirring dropwise until a congo red end point was reached at which time a white precipitate formed. The mixture was immediately filtered and the precipitate washed with cold water and dissolved in chloroform; the chloroform layer was separated from the small amount of water present, diluted with twice the volume of hexane, and cooled in Dry Ice. A white crystalline compound formed and was collected giving 0.400 g, mp 81.5–83.0°, of 1-*aci*-nitro-4-phenylcyclohexane. The mother liquor was concentrated to one-third the volume and after cooling in Dry Ice gave an additional 0.100 g, mp 81.0–83.5°, of this material. The total yield of *aci*-nitro tautomer was 0.500 g (71.5%).

(12) This is in agreement with F. G. Bordwell and M. M. Vesting (*J. Am. Chem. Soc.*, **89**, 3906 (1967)) who found, similarly, that 1-*aci*-nitro-4-*t*-butylcyclohexane tautomerizes in acetic acid to yield predominantly the *trans* isomer.

(13) *Cf.* the concept of product approach control of W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).

(14) The *aci*-nitro to nitro tautomerization is considerably less exothermic than the enol to ketone parallel. Hence, the *aci*-nitro to nitro transition state will be much further along the reaction coordinate toward nitro compound than the enol to ketone transition state is toward ketone.

(15) A. Bowers, M. B. Sanchez, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 3702 (1959).

(16) A. T. Nielson, *J. Org. Chem.*, **27**, 2001 (1962).

(17) All melting points were taken on an apparatus checked with known compounds.

(18) The general method of W. D. Emmons and A. S. Pagano (*J. Am. Chem. Soc.*, **77**, 4557 (1955)) was used.

(19) H. E. Ungnade, *J. Org. Chem.*, **13**, 3614 (1948).

The physical data were as follows: infrared ($CHCl_3$) 2.8–4.5 (broad, OH), 6.01 (C=N), 6.46, 6.69, 8.60, 9.95, 10.03, and 14.30 μ; nmr ($CDCl_3$) τ −1.25 singlet (1 H, hydroxyl), 2.75 singlet (5 H, aromatic), and 6.32–8.83 multiplet (9 H, cyclohexyl).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.21; H, 7.38. Found: C, 70.38; H, 7.49.

cis-1-Nitro-4-phenylcyclohexane (0.700 g, 3.71 mmol), treated in the same manner as above, gave 0.236 g (33.7%) of the *aci*-nitro tautomer, mp 81.5–83.0°. The physical data were identical with that of the *aci*-nitro tautomer formed from the *trans*-nitro isomer.

Tautomerization of *aci*-Nitro Compound with Lithium Acetate–Acetic Acid Buffer. To 42 mg of 1-*aci*-nitro-4-phenylcyclohexane was added 5.00 ml of a buffer solution composed of 6.12 g of lithium acetate, 0.36 g of acetic acid, 30.0 ml of 95% ethanol, and 3.90 ml of water. The resulting solution was stirred for 15 min and then diluted with 15.0 ml of water and ether extracted. The ether extract was washed with 5% sodium bicarbonate and water, dried, and concentrated *in vacuo* giving 39 mg of an oil. The infrared showed the presence of only *cis*- and *trans*-1-nitro-4-phenylcyclohexanes, and quantitative infrared showed it to contain 37.3% of the *cis*-nitro isomer.

Tautomerization of *aci*-Nitro Compound with Collidine–Collidine Hydrochloride Buffer. To 45 mg of the *aci*-nitro tautomer was added 5.00 ml of a buffer solution composed of 4.00 g of collidine, 0.35 g of collidine hydrochloride, 20.00 ml of 95% ethanol, and 2.60 ml of water. The resulting solution was stirred for 15 min under nitrogen and then diluted with 15 ml of water and ether extracted. The ether extract was washed with 5% hydrochloric acid and water, dried, and concentrated *in vacuo* giving 39 mg of an oil which was shown to contain 60.5% of the *cis* isomer.

Tautomerization of *aci*-Nitro Compound with 2-Methylquinoline–2-Methylquinoline Hydrochloride Buffer. To 49 mg of the *aci*-nitro tautomer was added 5.00 ml of a buffer solution composed of 6.00 g of 2-methylquinoline, 0.52 g of 2-methylquinoline hydrochloride, 30.00 ml of 95% ethanol, and 3.90 ml of water. The resulting solution was stirred for 15 min and worked up in the same manner described above for the collidine–collidine hydrochloride buffered tautomerization. An oil (46 mg) remained which was shown to contain only the isomeric nitro compounds and by quantitative infrared analysis to contain 61.3% of the *cis*-nitro isomer.

Tautomerization of *aci*-Nitro Compound with Pyridine–Pyridine Hydrochloride Buffer. The same method as used above was employed. The buffer solution was composed of 4.00 g of pyridine, 0.35 g of pyridine hydrochloride, 20.00 ml of 95% ethanol, and 2.6 ml of water. After work-up an oil remained which was shown to contain only the isomeric nitro compounds and by quantitative infrared analysis to contain 52.9% of the *cis*-nitro isomer.

Stability of *cis*-1-Nitro-4-phenylcyclohexane to the Conditions Used for Tautomerization. To 49 mg of *cis*-1-nitro-4-phenylcyclohexane was added 2.00 ml of acetone and 5.00 ml of the lithium acetate–acetic acid buffer described above and the resulting solution stirred for 15 min under nitrogen. Quenching with water and base work-up as described above gave 46 mg of a white solid which was shown by quantitative infrared analysis to be pure *cis*-nitro isomer.

Similarly, 49 mg of the *cis*-nitro compound was placed in 2.00 ml of acetone and 5.00 ml of the collidine–collidine hydrochloride buffer described above and the resulting solution stirred for 15 min under nitrogen. Quenching with water and acid work-up as described above gave 46 mg of a white solid which was shown by quantitative infrared analysis to be pure *cis*-nitro compound.

Equilibration of the 1-Nitro-4-phenylcyclohexanes. A mixture of 50 mg of sodium bicarbonate in 50 ml of 95% ethanol was heated to boiling and the hot ethanol solution decanted from the undissolved solid. To 5.00 ml of this solution was added 45 mg of *cis*-1-nitro-4-phenylcyclohexane with reflux for 4.0 hr. It was then quenched with 50 ml of water and ether extracted. The ether extract was dried and concentrated *in vacuo* yielding 45 mg of a white semisolid which was shown by quantitative infrared analysis to contain 20.9% of the *cis*-nitro isomer.

1-Acetyl-4-phenylcyclohex-3-ene. A mixture of 19.50 g (0.150 mol) of 2-phenylbutadiene,[20] 13.05 g (0.196 mol) of methyl vinyl ketone (containing 1% hydroquinone), and 30 ml of benzene was refluxed under nitrogen for 6.0 hr. The reaction mixture upon concentration *in vacuo* gave 28.72 g of a pale yellow oil which was distilled and afforded 11.58 g (38.8%), bp 125–133° (0.4 mm), of a crystallizing oil. Recrystallization from pentane gave pure 1-acetyl-4-phenylcyclohex-3-ene, mp 39.0–40.5°. The physical data for this compound were as follows: infrared ($CHCl_3$ and CS_2) 5.83, 6.27, 6.70, 13.25, and 14.41 μ; nmr (CCl_4) τ 2.80 singlet (5 H, aromatic), 4.00 singlet (1 H, vinyl), 7.91 singlet (3 H, methyl), and 7.22–8.66 multiplet (7 H, cyclohexyl).

Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.84; H, 8.12.

***cis*- and *trans*-1-Acetyl-4-phenylcyclohexanes.** A solution of 9.449 g (0.047 mol) of 1-acetyl-4-phenylcyclohex-3-ene in 60 ml of ethyl acetate was hydrogenated at atmospheric pressure using 0.245 g of platinum dioxide catalyst. After 1053 cc (0.047 mol after correction) of hydrogen had been consumed the uptake slowed. The reaction was stopped and the catalyst removed by filtration. Concentration of the filtrate *in vacuo* gave 9.812 g of a yellow oil which was chromatographed on a 5.0 × 70 cm silica gel (Davison grade 950, 60–200 mesh) column slurry packed in 4% ether–hexane. Elution was with 3.5 l. of 4% ether–hexane, 2.5 l. of 6% ether–hexane, and 9.5 l. of 8% ether–hexane; 250-ml fractions were collected. Fractions 8–10 and 17–26 contained 0.145 g and 0.147 g, respectively, of unidentifiable noncrystallizing oils. Fractions 28–36 contained 5.151 g of a low-melting white solid found by later equilibration studies to be *cis*-1-acetyl-4-phenylcyclohexane. Recrystallization from pentane gave 4.325 g (45.5%), mp 53.0–55.0°, of the *cis* isomer. The physical data were as follows: infrared (CS_2) 5.83, 8.81, 13.30, 14.36, and 15.17 μ; nmr (CCl_4) τ 2.80 singlet (5 H, aromatic), 7.89 singlet (3 H, methyl), and 7.26–8.50 multiplet (10 H, cyclohexyl).

Anal. Calcd for $C_{14}H_{16}O$: C, 83.12; H, 8.97. Found: C, 82.89; H, 9.03.

Fractions 37–42 contained 1.075 g of a noncrystallizing oil found to be a mixture of *cis* and *trans* ketones. Fractions 43–55 contained 1.737 g of a low-melting white solid which was later found to be *trans*-1-acetyl-4-phenylcyclohexane. Recrystallization from pentane yielded 1.214 g (12.9%), mp 54.0–56.0°, of the *trans* isomer with the following physical data: infrared (CS_2) 5.83, 7.00, 8.01, 13.30, 14.36, 14.36, and 15.78 μ; nmr (CCl_4) τ 2.79 singlet (5 H, aromatic), 7.89 singlet (3 H, methyl), and 7.46–8.93 multiplet (10 H, cyclohexyl).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.36; H, 9.05.

Quantitative Infrared Analysis of Mixtures of *cis*- and *trans*-1-Acetyl-4-phenylcyclohexanes. The same analytical technique described above was employed. In this analysis the superscripts refer to the wavelengths λ' 8.82 μ and λ'' 8.01 μ. F was determined empirically from three known mixtures as shown in Table IV and was found to have an average value of 0.950. All spectra involved in this analysis were obtained on a Beckman IR 8 spectrophotometer at a total concentration of 40 mg/0.30 ml of CS_2. The calibration runs indicate an estimated inaccuracy of ±2.0% *cis* isomer due to infrared uncertainties.

Table IV. Infrared Analysis of a Mixture of *cis*- and *trans*-1-Acetyl-4-phenylcyclohexanes

Actual % *cis* isomer	D' (8.82 μ)	D'' (8.01 μ)	Q (calcd)	R (act.)	F (calcd)	Calcd % *cis* isomer
100.0	0.432	0.076	...	...	...	...
75.0	0.357	0.116	3.516	3.00	0.835	77.0
50.0	0.287	0.167	1.062	1.00	0.942	50.3
25.0	0.223	0.222	0.344	0.33	0.960	24.6
0.0	0.560	0.277	...	...	...	...

Equilibration of the 1-Acetyl-4-phenylcyclohexanes. To a solution of sodium ethoxide prepared from 40 mg of sodium in 5.0 ml of absolute ethanol was added 99 mg of *cis*-1-acetyl-4-phenylcyclohexane and the resulting mixture stirred at room temperature for 8.0 hr in a flask fitted with a carbon dioxide exclusion tube. It was then poured into 50 ml of water and ether extracted. The ether extract was dried and concentrated *in vacuo* giving 95 mg of a white solid which was shown by quantitative infrared analysis to contain 8.0% of the *cis* isomer.

1-Bromo-1-acetyl-4-phenylcyclohexanes. To a solution of 2.999 g (14.8 mmol) of *cis*-1-acetyl-4-phenylcyclohexane in 60.0 ml of

(20) C. Price, F. Benton, and C. Schmidle, *J. Am. Chem. Soc.*, 71, 2860 (1949).

glacial acetic acid was added to 2.660 g (16.2 mmol) of bromine. After stirring for 8.0 min the reaction mixture turned from red-brown to a lemon yellow color and was immediately poured into 150 ml of water; this solution was extracted with 1:1 ether–pentane. The organic extracts were dried and concentrated *in vacuo* yielding 4.138 g of a pale yellow oil which was chromatographed on a 91 × 2.0 cm silica gel (Davison grade 950, 60–200 mesh) column slurry packed with 5% ether–hexane. Elution was with 2 l. of 4% ether–hexane, 5.75 l. of 6% ether–hexane, 1.25 l. of 8% ether–hexane, and 1.25 l. of 10% ether–hexane; 250-ml fractions were collected. Fractions 16–17 and 27–29 contained 0.032 and 0.048 g, respectively, of unidentifiable noncrystallizing oils. Fractions 7–15 contained 2.693 g of a white solid which, upon recrystallization from pentane, yielded 2.301 g (55.4%), mp 56.0–58.0°, of what was later shown (*vide infra*) to be 1-bromo-*cis*-1-acetyl-4-phenylcyclohexane. Physical data were as follows: infrared (CS_2) 5.83, 7.38, 9.00, and 12.35 μ; nmr (CCl_4) τ 2.82 singlet (5 H, aromatic), 7.62 singlet (3 H, methyl), and 7.10–8.80 multiplet (9 H, cyclohexyl).

Anal. Calcd for $C_{14}H_{17}BrO$: C, 59.80; H, 6.09; Br, 28.42. Found: C, 59.50; H, 6.10; Br, 28.84.

Fractions 18–26 contained 1.268 g of a white solid which, upon recrystallization from pentane, yielded 1.135 g (27.3%), mp 71.5–73.0°, of 1-bromo-*trans*-1-acetyl-4-phenylcyclohexane with the following physical data: infrared (CS_2) 5.83, 8.30, 9.12, and 12.11 μ; nmr (CCl_4) τ 2.81 singlet (5 H, aromatic), 7.59 singlet (3 H, methyl), and 7.20–8.50 multiplet (9 H, cyclohexyl).

Anal. Calcd for $C_{14}H_{17}BrO$: C, 59.80; H, 6.09; Br, 28.42. Found: C, 59.79; H, 6.53; Br, 28.33.

Zinc Debrominations. In a typical run 56 mg of either the *cis* or *trans* isomer of 1-acetyl-1-bromo-4-phenylcyclohexane was stirred in a given solvent with 300 mg of zinc dust and a proton source under a nitrogen atmosphere. After completion of the reaction the mixture was filtered, poured into water, and extracted with ether. The ether was dried and concentrated *in vacuo*. Quantitative ir analysis of the products gave the results summarized in Table I.

Hydriodic Acid Debromination of 1-Bromo-*cis*-1-acetyl-4-phenylcyclohexane. To 56 mg of 1-bromo-*cis*-1-acetyl-4-phenylcyclohexane in 2.0 ml of acetone was added 0.10 ml of 47% hydriodic acid. Iodine was liberated instantaneously, and after 0.5 hr the reaction mixture was poured into 15.0 ml of water containing 1.00 g of sodium sulfate and extracted with ether. The ether extract was dried and concentrated *in vacuo* leaving 42 mg of an oil which was shown by quantitative ir analysis to contain 41.3% of *cis*-1-acetyl-4-phenylcyclohexane.

Hydriodic Acid Debromination of 1-Bromo-*trans*-1-acetyl-4-phenylcyclohexane. To 56 mg of the *trans*-bromo ketone was added 0.1 ml of 47% hydriodic acid. Iodine was liberated more slowly than in the *cis*-bromo ketone case (*ca.* 10 sec before a red-brown color appeared). Quantitative infrared analysis of the product (41 mg) showed it to contain 40.0% of the *cis* ketone.

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The Photochemistry of Benzobarrelene. Mechanistic and Exploratory Photochemistry. XXXV[1]

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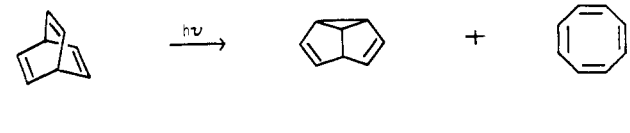
Abstract: The acetone-sensitized rearrangement of 1,4-dihydro-1,4-ethenonaphthalene (benzobarrelene) (**9**) afforded 3,4-benzotricyclo[3.3.0.0^{2,8}]octa-3,6-diene (benzosemibullvalene) (**16**) whose structure was established by spectral and degradative means. It was found that N-deuterated lithium cyclohexylamide in N,N-dideuteriocyclohexylamine selectively exchanged the aryl and vinyl protons of benzobarrelene. Photolysis of perdeuterated benzobarrelene with undeuterated bridgehead positions (**24**) afforded perdeuterated benzosemibullvalene with protons at carbons 2 and 5 (**25**). Of the various mechanisms possible for the benzobarrelene to benzosemibullvalene transformation, the labeling result uniquely identifies the process as utilizing the divinylmethane pathway reported earlier for barrelene (**1**). Furthermore, of two *a priori* possibilities, initial vinyl–vinyl and benzo–vinyl bonding, the former was shown to be preferred. Direct irradiation of benzobarrelene gave only benzocyclooctatetraene (**17**). Intersystem crossing of benzobarrelene is concluded to be slow. Direct irradiation of bridgehead hydrogen labeled benzobarrelene afforded benzocyclooctatetraene with the hydrogen label mainly at C-4 and C-7 (**27**) plus a small amount of the label at C-3 and C-8 (**28**). Irradiation of perdeuterated benzosemibullvalene with hydrogen label in the C-2 and C-5 positions gave benzocyclooctatetraene with the hydrogens at carbons 3 and 8 (**28**). This is in contrast with the results of the direct irradiation of perdeuterated benzobarrelene. It is concluded that there are two routes to benzocyclooctatetraene: (a) a triplet pathway from benzobarrelene to benzosemibullvalene followed by direct irradiation of the benzosemibullvalene involving cleavage of the 2–8 and 1–5 bonds; (b) a singlet route initiated predominantly by four-center cycloaddition of a vinyl group to the benzo group plus a small amount from vinyl–vinyl cycloaddition. The various transformations are considered from a mechanistic viewpoint.

Previously, we reported the rearrangement of barrelene (**1**) to semibullvalene (**2**) and cyclooctatetraene (**3**) on acetone photosensitization[2] as shown in Chart I. The mechanism of the barrelene to semibullvalene transformation was determined in our subsequent studies[3] using vinyl-deuterated barrelene (**4**). The reaction was noted[3] (Chart II) to be an

Chart I. Photorearrangement of Barrelene



1 2 3

(1) (a) For our preliminary communication, note: *J. Am. Chem. Soc.*, **90**, 4191 (1968); (b) paper XXXIII of the series: H. E. Zimmerman, K. G. Hancock, and G. C. Licke, *ibid.*, **90**, 4892 (1968).

(2) H. E. Zimmerman and G. L. Grunewald, *ibid.*, **88**, 183 (1966).