Conformational Analysis. III.[1,2] Electrostatic Repulsion as a Factor in the Conformational Preference of Substituted Unsaturated Bicyclic Compounds

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The conformational preference of the nitro group in the 5-position of bicyclo[2.2.1]heptene and bicyclo[2.2.2]-octene has been determined by base equilibration using potassium *t*-butoxide in *t*-butyl alcohol. Similarly the 5-carbomethoxy compounds have also been equilibrated using sodium methoxide in methanol. The *exo/endo* ratio for 5-nitro- and 5-carbomethoxybicyclo[2.2.1]heptene are 1.80 and 1.06, respectively, at 75°. The *exo/endo* ratios for 5-nitro- and 5-carbomethoxybicyclo[2.2.2]octene are 0.44 and 0.46, respectively, at 75°. The difference in the conformational preferences of the nitro and carbomethoxy groups in the bicyclo[2.2.1]heptene system is postulated to be the result of an electrostatic repulsion between the substituent and the π-electrons. That this repulsion term is less important in bicyclo[2.2.2]octene is the result of increased distance between the π-electrons and the substituent.

The conformational preference of substituents in bicyclic molecules has received little attention compared to the extensive work on the cyclohexane system. This paucity of information is incongruous considering the unique structural properties of bicyclic compounds and the current interest in strained ring systems. The relative rigidity of bicyclic compounds and consequent limitations on the orientations that the atoms can assume, coupled with numerous possible structural variations, make these compounds extremely valuable models for the evaluation of nonbonded interactions. Nonbonded interactions as a function of distance should be directly available by variation of the bicyclic skeleton.

The methods of evaluating the conformational preference of substituents in bicyclic compounds are limited compared to the cyclohexane system. Numerous methods which are dependent on a comparison of physical or chemical properties of monosubstituted cyclohexanes with those of the corresponding locked *cis*- and *trans*-4-*t*-butylcyclohexane derivatives cannot be applied to rigid bicyclic compounds. It is therefore necessary either to determine the thermodynamic functions of each epimer or to devise a method of interconversion of epimers under equilibrium conditions.

In order to evaluate the factors controlling the conformational preference of substituents in bicyclic systems, our initial work has been in the strain-free [2.2.2] and strained [2.2.1] systems. Though numerous compounds of these ring systems are known owing to their ease of preparation by the Diels–Alder reaction, very little quantitative information concerning the conformational preference of substituents is available. The conformational preference of the carbomethoxy group in the isomeric 5-carbomethoxybicyclo[2.2.1]heptenes and 2-carbomethoxybicyclo[2.2.1]heptanes has been determined by base equilibration and v.p.c. analysis.[3] However, most other studies in which equilibrations of bicyclic compounds have been employed have not been carried out for this specific purpose. The primary purpose has been to enrich a mixture of isomers in one component and it is uncertain whether these values are equilibrium distributions. Roberts[4] treated the bicyclo[2.2.1]hepten-5-ols with sodium and fluorenone in refluxing toluene and obtained 47% of the *exo* isomer as recovered product. LeBel[5] enriched a mixture of bicyclo[2.2.2]octen-5-ols using aluminum isopropoxide and obtained a 34:66 ratio of *exo* to *endo* alcohol. However, in a footnote in the Experimental a 59:41 ratio is reported.[6] The latter value was obtained using aluminum *t*-butoxide in refluxing benzene containing a trace of fluorenone. The subject of equilibration of bicyclic alcohols and the problems associated with such studies has been discussed by Wilcox.[7]

In the course of this investigation it has been noted that the presence of π-electrons leads to anomalous results if the substituent contains nonbonded electrons. Cope[3] equilibrated the isomeric 5-carbomethoxybicyclo[2.2.1]heptanes "with the aim of obtaining information concerning the relative steric effects of an ethanol and ethylenic bridge and the interaction between the π-orbital of the double bond and C_5-*endo* substituents." In this paper the effect of the π-electrons in bicyclo[2.2.1]heptene and bicyclo[2.2.1]octene on the nitro and the carbomethoxy groups will be examined and discussed in terms of a repulsive electrostatic interaction.

Results

Equilibration of *endo*- and *exo*-5-carbomethoxybicyclo[2.2.1]heptene was accomplished using 0.10 *M* sodium methoxide in methanol. The concentration of substrate was 0.03 *M*. The equilibrium values expressed as *exo/endo* are given in Table I.[8] Studies at temperatures other than 75 and 100° were not carried out as the value for the equilibrium constant of near unity made the thermodynamic parameters of doubtful significance. Equilibration of *endo*- and *exo*-5-carbomethoxybicyclo[2.2.2]octene (IIa and IIb) was carried out under similar experimental conditions. The equilibrium values for the *exo/endo* ratio are given in Table I.

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[1] Part II: R. J. Ouellette, *J. Am. Chem. Soc.*, **86**, 4378 (1964).

[2] Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

[3] A. C. Cope, E. Ciganek, and N. A. LeBel, *J. Am. Chem. Soc.*, **81**, 2799 (1959).

[4] J. D. Roberts, C. C. Lee, and W. H. Saunders, *ibid.*, **77**, 3034 (1955).

[5] N. A. LeBel and J. E. Huber, *ibid.*, **85**, 3193 (1963).

[6] The authors are indebted to a referee who brought this paper to our attention. However, only the 34:66 ratio was noted and caused us considerable discomfort in attempting to rationalize the ideas to be presented in the Discussion with the results of LeBel. It was with relief that a close examination of the paper indicated that the 34:66 ratio is not an equilibrium value.

[7] C. F. Wilcox, Jr., M. Sexton, and M. F. Wilcox, *J. Org. Chem.*, **28**, 1079 (1963).

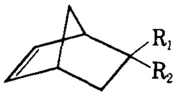
[8] The values reported by Cope[3] for 5-carbomethoxybicyclo[2.2.1]heptene are somewhat lower. However, the conditions employed indicate that a slurry was utilized or, if complete solution occurred, the concentrations were considerably higher than employed in this work.

TABLE I

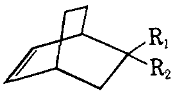
Compd.	Temp., °C.	K (*exo/endo*)[a]
5-Carbomethoxybicyclo[2.2.1]heptene	100.0	1.09 ± 0.02
	75.0	1.05 ± 0.02
5-Carbomethoxybicyclo[2.2.2]octene	100.0	0.45 ± 0.01
	75.0	0.46 ± 0.01
5-Nitrobicyclo[2.2.1]heptene	100.0	1.81 ± 0.03
	75.0	1.80 ± 0.03
	50.0	1.79 ± 0.03
5-Nitrobicyclo[2.2.2]octene	100.0	0.42 ± 0.02
	75.0	0.44 ± 0.02
	50.0	0.39 ± 0.02

[a] See footnote 9.

It was necessary to equilibrate the 5-nitrobicyclo[2.2.1]heptenes (Ic and Id) and 5-nitrobicyclo[2.2.2]octenes (IIc and IId) using lower base concentrations. The nitro compounds are sufficiently acidic to exist predominantly as the conjugate bases. When the concentration of *endo*-5-nitrobicyclo[2.2.1]heptene was 0.03 *M* and the base system was 0.10 *M* potassium *t*-butoxide in *t*-butyl alcohol, the observed *exo/endo* ratio is approximately 0.05. This value is established rapidly and is unchanged with time. That this value is not a true equilibrium constant, was indicated by lowering the base concentration to 0.003 *M*. The *exo/endo* ratio is 1.80 at 75° under these conditions. All nitro compounds were equilibrated at low base concentrations to obtain the equilibrium constants (see Discussion). The equilibrium *exo/endo* ratio for the isomers of 5-nitrobicyclo[2.2.1]heptene and 5-nitrobicyclo[2.2.2]octene are given in Table I.[9]



Ia, R_1 = H; R_2 = CO_2CH_3
b, R_1 = CO_2CH_3; R_2 = H
c, R_1 = H; R_2 = NO_2
d, R_1 = NO_2; R_1 = H



IIa, R_1 = H; R_2 = CO_2CH_3
b, R_1 = CO_2CH_3; R_2 = H
c, R_1 = H; R_2 = NO_2
d, R_1 = NO_2; R_2 = H

Discussion

It will be assumed in this discussion that the nitro and carbomethoxy groups are of essentially the same steric size in a system where other polar sites are absent. However, there exists no direct experimental evidence in support of the assumed equivalence of the nitro and carbomethoxy groups other than presented in this paper. The bond angles and bond lengths of the nitro group in nitromethane are known.[10,11] A direct equilibration of the appropriate nitro compounds in the now standard cyclohexyl system has not been carried out in spite of the availability of the necessary compounds.[12] The n.m.r. resonance signal for the α-hydrogen in nitrocyclohexane has been examined and it has been concluded that the nitro group is exclusively equatorial.[13] However, this conclusion was based solely on agreement between the observed spectrum and a calculated spectrum for the equatorial conformer. The observed chemical shift for the methine multiplet of nitrocyclohexane is τ 5.72. Huitric[12] examined *cis*- and *trans*-4-*t*-butylnitrocyclohexane 2 years earlier and found that the methine hydrogens for the *cis* and *trans* isomers occur at τ 5.37 and 5.77, respectively. While the experimental results of both groups of workers certainly should not be used to calculate the conformational preference of the nitro group, it would appear that nitrocyclohexane exists to a small extent in the axial conformation.

Both 5-nitrobicyclo[2.2.2]octene and 5-carbomethoxy-[2.2.2]octene show a clear preference for the *endo* position compared with 5-nitrobicyclo[2.2.1]heptene and 5-carbomethoxy[2.2.1]heptene. This preference is undoubtedly due to the increased interaction of substituents in the *exo* position with the hydrogen in the 7-position in bicyclo[2.2.2]octene compared with the 7-position in bicyclo[2.2.1]heptene.[14] The close agreement between the equilibrium constants for the nitro and carbomethoxy groups in the bicyclo[2.2.2]octene system tends to support the assumption that the two groups are of the same steric size.

There is a substantial difference in the conformational preference of the nitro and carbomethoxy group in the bicyclo[2.2.1]heptene system. The controlling factor may be an electrostatic interaction involving a repulsion of the substituent by the π-electrons. The high electron density of the oxygen atoms on the nitro group compared to the carbomethoxy group should lead to increased repulsion, thus destabilizing the *endo*-nitro isomer relative to the *endo*-carbomethoxy isomer. That this repulsion is not observed in the bicyclo[2.2.2]octene system is evident by examining models. The angle of the plane defined by atoms 1, 2, 3, and 4 and the plane defined by atoms 4, 5, 6 and 1 is smaller in bicyclo[2.2.1]heptene than in bicyclo[2.2.2]octene. The "plane" of the π-electrons is directed toward the substituent in the 5-*endo* position in bicyclo[2.2.1]heptene, whereas in bicyclo[2.2.2]octene the "plane" of the π-electrons becomes more mutually parallel with the plane of the *endo* bonds in bicyclo[2.2.2]octene.

While there is an obvious difference in the equilibrium constants for the equilibration of the nitro- and carbomethoxybicyclo[2.2.1]heptenes, the energy difference amounts to only 0.3 kcal./mole. The equilibrations of the compounds appear to be largely entropy controlled. However, with equilibrium constants in the order of magnitude reported, an apportionment of ΔG between ΔH and ΔS is difficult to make. The thermodynamic functions reported by Cope for the *endo* → *exo* conversion of the 5-carbomethoxybicyclo[2.2.1]heptenes and the 2-carbomethoxybicyclo[2.2.1]heptanes also reflect this entropy effect. The enthalpy differences were given as zero and the entropy differences as −0.12 cal./mole and +1.71 cal./deg. for the unsaturated and the saturated systems, respectively. Assuming that the difference in enthalpy between each pair of epimers studied in this paper is approximately

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[9] The estimates of error represent an average of individual values obtained in three independent equilibrations. The values for the nitro compounds cannot be considered true equilibrium constants as a fraction of the *endo* isomer is formed as a result of kinetically controlled protonation in the quenching process. See Discussion.

[10] L. O. Brockway, J. Y. Beach, and L. Pauling, *J. Am. Chem. Soc.*, **57**, 2693 (1935).

[11] E. Tannenbaum, R. J. Meyers, and W. D. Gwinn, *J. Chem. Phys.*, **25**, 42 (1956).

[12] A. C. Huitric and W. F. Trager, *J. Org. Chem.*, **27**, 1926 (1962).

[13] W. Hofman, L. Stefaniak, J. Urbanski, and W. W. Tanowski, *J. Am. Chem. Soc.*, **86**, 554 (1964).

[14] The interaction between a substituent in the *exo* position of bicyclo[2.2.2]octene and the 7-position is probably similar to the 1,3-boat-axial interaction in cyclohexane. The distance separating the substituent in the *exo* position of bicyclo[2.2.1]heptene and the 7-position is larger than in bicyclo[2.2.2]octene. However, it is necessary to warp the Dreiding models considerably to construct bicyclo[2.2.1]heptene and the actual difference cannot be obtained unambiguously.

zero, the entropy differences for the *endo* → *exo* conversion are +0.1, −1.6, +1.2, and −1.7 cal./deg. for 5-carbomethoxybicyclo[2.2.2]heptene, 5-carbomethoxybicyclo[2.2.2]octene, 5-nitrobicyclo[2.2.1]heptene, and 5-nitrobicyclo[2.2.2]octene, respectively. Any entropy difference between the isomers of 5-nitrobicyclo[2.2.1]-heptene can be rationalized in terms of the proposed π-electron repulsion of the oxygen atoms. The repulsion should result in a restriction in the free rotation of the nitro group. Similarly some restrictions of free rotation would be expected in *exo*-5-nitrobicyclo[2.2.2]-octene and *exo*-5-carbomethoxybicyclo[2.2.2]octene as the hydrogen in the 7-position is in close proximity to substituents in the 5-position.

It was noted in the section entitled Results that it is necessary to equilibrate the nitro compounds utilizing low base concentrations. At high base concentrations (0.10 *M*) a low *exo*/*endo* ratio (0.05) is observed even after as short a time as 15 min. at 75°. Under these conditions the nitro compound probably exists solely as the conjugate base. The observed *exo*/*endo* ratio is therefore a reflection of the kinetically controlled attack of the protonating species in the quenching process. Flanagan[15] determined the rate of proton abstraction of the acidic hydrogen of *exo*- and *endo*-5-nitrobicyclo[2.2.1]heptene. The *exo* hydrogen is abstracted approximately 20 times faster than the *endo* hydrogen. While there are considerable differences in experimental conditions between Flanagan's and this work, a similar difference in rates should be observed for the reverse reaction.

The values reported for the nitro compounds in Table I are certainly distorted in favor of the *endo* isomer as result of kinetically controlled protonation in the quenching process. In order to reduce this distortion below that of experimental error with complete certainty, it would be necessary to work at base concentrations that are less than 1% of that of the substrate. However, while the reported values might be modified by utilizing lower base concentrations, the difference between the nitro- and carbomethoxybicyclo[2.2.1]heptenes will remain larger than the difference between the nitro- and carbomethoxybicyclo-[2.2.2]octenes.

If the nitro and carbomethoxy groups are indeed sterically equivalent, then the conformational preferences of the two groups in the bicyclo[2.2.1]heptane system would be identical. While the necessary carbomethoxy compounds are readily separable by v.p.c., the corresponding nitro compounds are not separable even on an analytical scale. Work to devise an analytical procedure is continuing.[16]

This work is being extended to incorporate hetero atoms in the bicyclic skeleton to determine the magnitude of the interaction between two sites containing nonbonded electrons.

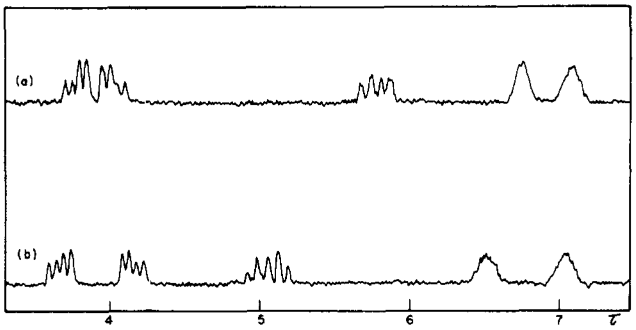

Figure 1.—Proton n.m.r. spectra of (a) *exo*-5-nitrobicyclo[2.2.1.]-heptene and (b) *endo*-5-nitrobicyclo[2.2.1.] heptene.

Experimental

All compounds were prepared by the Diels–Alder reaction of the appropriate diene and dienophile and possessed the reported physical constants.[3,15,17-19] Separation of the isomers was accomplished by preparative vapor phase chromatography on a 20-ft. 30% SE-30 column. The *endo* isomer had the longer retention time in all cases.

The vinyl hydrogen region of the n.m.r. spectrum of each compound was characteristic and confirmed the assigned stereochemistry of all compounds. The difference in the chemical shift of the two vinyl hydrogens of the *endo* isomer is larger than that for the *exo* isomer. The low-field n.m.r. spectra of *exo*-5-nitrobicyclo[2.2.1]heptene and *endo*-5-nitrobicyclo[2.2.1]heptene are given in Figure 1. These spectra also serve to illustrate the purity of the individual isomers.

Anhydrous methanol was obtained by distillation from calcium hydride. The *t*-butyl alcohol was dried over Linde Molecular Sieves and then distilled from fresh sieves. Commercial sodium methoxide and potassium *t*-butoxide were used without purification.

All equilibrations were performed using 10 ml. of the appropriate solvent and the concentration of substrate was approximately 0.03 *M*. The potassium *t*-butoxide solutions were 0.003 *M* in the base. The sodium methoxide solutions were approximately 0.10 *M* in the base. Sealed ampoules were placed in constant-temperature baths at 50.0, 75.0, and 100.0°. The baths were maintained at the indicated temperature within ±0.03°.

After sufficient time for equilibration had elapsed, the ampoules were removed; the sample was quenched by breaking the ampoules in dilute aqueous acetic acid. The aqueous layer was extracted three times with low-boiling petroleum ether. The petroleum ether extracts were combined, dried over magnesium sulfate, and concentrated.

Analyses were performed utilizing Aerograph A-90-P and A-600-B instruments. Diethylene glycol succinate, butanediol succinate, and QF-1 columns were found to be suitable for analytical purposes. The compounds investigated exhibited only very slight tailing on the columns employed and the peaks were essentially symmetrical. The peak areas were determined by planimetry. Each equilibrium mixture was run a minimum of three times to determine the reproducibility of the gas chromatographic analysis. Equilibrium constants were reproducible to 1%. Each equilibration was carried out a minimum of three times. The variance between individual runs was less than 2% in the calculated equilibrium constant. Appropriate controls were performed to show the quantitative nature of the entire analytical procedure.

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[15] P. W. K. Flanagan, Ph.D. Thesis, The Ohio State University 1957.

[16] Analysis of an equilibrium mixture by n.m.r. indicates that the *exo*/*endo* ratio is between 2 and 4.

[17] J. D. Roberts, E. R. Trumbull, Jr., W. Bennett, and R. Armstrong, *J. Am. Chem. Soc.*, **72**, 3116 (1950).

[18] W. R. Boehme, E. Schipper, W. G. Scharpf, and J. Nichols, *ibid.*, **80**, 5488 (1958).

[19] J. D. Roberts, C. C. Lee, and W. H. Saunders, Jr., *ibid.*, **76**, 4501 (1954).