^{17}O NMR Spectroscopy as a Tool for Studying Synthetic Oxygen Carriers Related to Biological Systems: Application to a Synthetic Single-Face Hindered Iron Porphyrin-Dioxygen Complex in Solution

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Abstract: The high-resolution ^{17}O NMR spectrum of a single-face hindered iron porphyrin-dioxygen complex in solution is reported. The spectrum exhibits two well-resolved resonances of the FeO_2 moiety, with different line widths, in agreement with an end-on structure proposed by Pauling for oxyhaemoglobin. Assignment of the two resonances was achieved on the basis of theoretical literature calculations. The experimental data can be explained in terms of bonding models in which the electrons of the FeO_2 moiety are totally paired, without a charge transfer $Fe(d^5)O_2^-$ superoxide configuration. An ozone-like bonding of the FeO_2 moiety is emphasized.

The structure of iron porphyrin-oxygen carriers, both natural and synthetic, and in particular the nature of the metal-oxygen bond have been debated for decades.[1,2] ^{17}O NMR spectroscopy can be considered as an excellent means to derive direct information about binding, structure, and reactivity of the coordinated molecular oxygen. This spectroscopic tool, despite several inherent disadvantages, i.e., low sensitivity, large line widths, and rolling base lines,[3] has attracted considerable interest as applied to dioxygen complexes due to the availability of oxygen-17 enriched gas and the extremely large chemical shift range (~1500 ppm) of the oxygen bonded to transition metals.[3,4] However, it was only recently that the first successful application of ^{17}O NMR to a peroxo-type oxygen was reported by Postel et al.[5] after several unsuccessful ^{17}O NMR studies of oxyhaemoglobin[6-8] and synthetic Vaska-type oxygen carriers.[9,10] Postel et al.,[5] however, painted a rather pessimistic picture of the future of ^{17}O NMR spectroscopy as applied to those O_2 derivatives that bind molecular oxygen reversibly, a prognosis that has recently been ruled out by the ^{17}O NMR observation of Vaska-type reversible complexes[11] (Lauterwein, J.; Gerothanassis I. P.; Schumacher, M., manuscript in preparation).

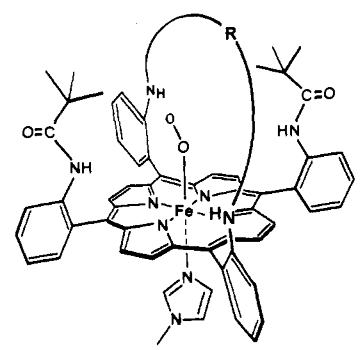
In the present work we report the first successful high-resolution ^{17}O NMR spectrum of the FeO_2 linkage of a dioxygen-1-methylimidazole-iron (d^6) porphyrin complex having one "handle" and two pivaloyl "pickets" as substituents (Chart I). This six-coordinated dioxygen adduct has been shown to be stable and reversible.[12,13]

Materials and Methods

The sample used in our study was prepared following a similar procedure to that published in ref 12. Gaseous oxygen containing 33 atom % oxygen-17 (Yeda-Stable Isotopes, Rehovot, Israel) was added in the toluene solution and the tube sealed (O_2 pressure ~5 atm). The NMR data were obtained with a Bruker AM-400 multinuclear spectrometer operating at 54.2 MHz for ^{17}O. No field/frequency locking system was used. The temperature was adjusted with use of a calibrated thermoresistance introduced into the magnet by way of a cylindrical tube containing the same solvent. Chemical shifts were measured relative to 1,4-dioxane determined in separate replacement experiments. At 34 °C the chemical shift of dioxane is identical with that of H_2O.

Data manipulations were carried out on an Aspect-3000 computer. The following spectral parameters were used: spectral width = 100 KHz; 90° pulse length = 30 μs; quadrature phase detection; acquisition time = 5 μs; preacquisition delay Δt = 100 μs when the normal 90° pulse train sequence was used; no relaxation delay; zero-filling to 2 K before FT. In order to eliminate acoustic ringing problems several spectra at low temperatures were recorded with either the extended spin-echo pulse sequence[14,15] or the reference-base line-substraction 90° pulse sequence[15,16] with practically negligible preacquisition and pulse delays. Because of the limited power of the 180° pulse over the entire spectral range, it was necessary to adjust the carrier frequency near the observed frequency. As a consequence, when the above pulse sequences were used, the ^{17}O NMR spectrum had to be recorded in two steps.

Chart I



R = CO-$(CH_2)_8$-CO

Results and Discussion

Chemical Shifts. Figure 1 shows the ^{17}O NMR spectrum of the compound of Chart I at 34 °C. The spectrum exhibits two distinct resonances at 1755 and 2488 ppm with an integral ratio of $I(1755)/I(2488)$ = 0.41 instead of the expected ratio (after

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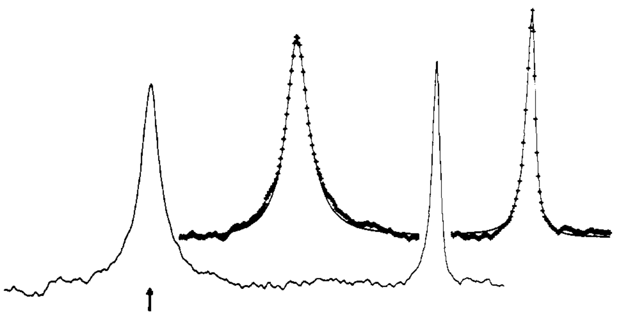
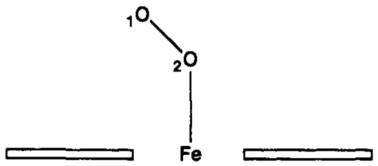


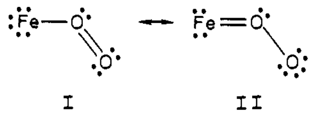
Figure 1. ^{17}O NMR spectrum (54.2 MHz) of the compound of Chart I with use of the normal 90° pulse train sequence. Concentration $\sim 10^{-2}$ M in toluene solution. Concentration of 1-methylimidazole $\sim 2.5 \times 10^{-1}$ M. $T = 34$ °C, number of scans $\sim 1.2 \times 10^6$, linebroadening filtering LB = 500 Hz, total experimental time ca. 100 min. Upper trace: Simulation of the ^{17}O resonances with a Lorentzian line shape. The symbol ↑ indicates the position of the transmitter carrier frequency.

Chart II. Pauling Model for the FeO_2 Moiety



correction of the amplitudes of the signals for the preacquisition delay used) of 1.75. This is due to a very pronounced off-resonance effect of the low-frequency absorption. This effect has been confirmed by recording spectra with the carrier frequency in the middle of the spectrum to symmetrize the offset effect. Both resonances are well outside of the established oxygen-17 chemical shift scale. The observation of two distinct resonances rules out the sideways triangular structure suggested by Griffith.[17] It suggests that the solution structure of the FeO_2 linkage is an end-on angular bond first proposed by Pauling.[18,19] This observation also rules out a rapid flipping of the O–O group between two bent conformers similar to that proposed for Co(bzacen)(py)(O_2).[20]

Nuclear screening constants are usually discussed with respect to contributions from a local diamagnetic and a local orbital paramagnetic term.[21] It is usually assumed that chemical shift differences are essentially induced by the latter term. Maricic et al.[6] calculated the local orbital paramagnetic contribution to the oxygen-screening constants of the oxygen nuclei of the FeO_2 linkage, treated as an isolated entity, in oxyhaemoglobin by the use of an average energy approximation.[22] The chemical shift difference $\Delta\delta = |\delta_1 - \delta_2|$ between the two oxygen atoms 1 and 2 (Chart II) was shown to be strongly dependent on the difference in their orbital populations. According to Pauling,[18,19,23] the FeO_2 linkage in HbO_2 is represented as a resonance hybrid of structures I and II. For structure II a difference of one electron between the two oxygens has been suggested by Pauling[18] and this results, according to Maricic et al.,[6] in a chemical shift $\Delta\delta \simeq 1500$ ppm. For structure I, $\Delta\delta \simeq 110$ ppm. Assuming an equal contribution of each hybrid structure then, $\Delta\delta = 805$ ppm which is in excellent agreement with the experimental value of 733 ppm. However, the chemical shifts δ_1 and δ_2 of the individual oxygens are too low compared with the experimental values.



I II

Velenic and Lynden-Bell[24] suggested that the methodology employed by Maricic et al.[6] is not suitable for the estimation of ^{17}O chemical shifts. They proposed that reasonable estimates can be obtained from an extended Hückel method.[25] The dioxygen ligand was considered as an independent unit and significant electron transfer between oxygen and iron was supposed not to occur. According to these calculations both oxygen nuclei exhibit chemical shifts to high frequency at least 1000 ppm relative to H_2O. The nucleus of the oxygen atom 2 near the iron atom (Chart II) was found to be more shielded than the nucleus of the terminal oxygen 1 by about 1400 to 1500 ppm. This shift, $\Delta\delta$, between the two nuclei is remarkably constant and independent of the value of the charge q on the oxygen nucleus 2 and the splitting ΔE of the degenerate π orbitals of the oxygen atom on complexing. However, the magnitudes of δ_1 and δ_2 critically depend on both values q and ΔE. Thus for $\Delta E = 1.04$ eV and $q = 0.19$ e, $\delta_1 = 3224$ ppm and $\delta_2 = 1647$ ppm; for $\Delta E = 0.20$ eV and $q = 0.029$ e, $\delta_1 = 13\,216$ ppm and $\delta_2 = 11\,844$ ppm. The former value is in reasonable agreement with our experimental data.

According to Velenic and Lynden-Bell[24] the calculated chemical shift difference ($\Delta\delta \sim 1500$ ppm) of the two nuclei is likely to be correct to ±500 ppm and would probably be enhanced by electron delocalization. Although it is difficult to know how much faith to put on assignments based on theoretical calculations with such a considerable amount of uncertainty, we should emphasize that the above assignment is also supported by the oxygen chemical shifts of the ozone molecule (see discussion below).

Line Widths: Nuclear Quadrupole Coupling Constants. In diamagnetic solutions the ^{17}O nucleus ($I = {}^5/_2$; quadrupole moment $Q = -0.026 \times 10^{28}$ m^2) relaxes predominantly by the quadrupolar mechanism. In the motional narrowing limit, $\omega_Q{}^2\,\tau_c{}^2 \ll 1$, which can be anticipated for small or medium size molecules in nonviscous liquids, the expression for the longitudinal (T_1) and transverse (T_2) relaxation times is given by[3]

$$\pi\Delta\nu_{1/2} = \frac{1}{T_{1Q}} = \frac{1}{T_{2Q}} = \frac{12\pi^2}{125}\left(1 + \frac{\eta^2}{3}\right)\left(\frac{e^2 q_{zz} Q}{h}\right)^2 \tau_c \qquad (1)$$

where ω_Q is the Larmor frequency for the ^{17}O nucleus in Hz, τ_c is the effective correlation time for reorientation at the site of the dioxygen moiety in s, $\Delta\nu_{1/2}$ is the resonance width at half-height in Hz, $\eta = (q_{xx} - q_{yy})/q_{zz}$ is the asymmetry parameter (the q_{xx}, q_{yy}, and q_{zz} are the principal components of the electric field gradient tensor), and $e^2q_{zz}Q/h$ is the nuclear quadrupole coupling constant (NQCC) in Hz. Equation 1 is valid only in the absence of line width broadening effects due to chemical exchange phenomena, and this has been confirmed by the equivalence of T_{1Q} and T_{2Q} of the low-frequency absorption at 0 °C.

To obtain values for NQCC requires an estimate of η and τ_c. The asymmetry parameter is usually ignored since the maximum error in the NQCC from this source would be about 5.5% even in exceptional cases with $\eta = 0.95$. An estimation of τ_c can, in principle, be achieved in two ways:[26] (i) calculation via the Stokes-Debye formula, and (ii) measurement of the relaxation times of a second nucleus cf. ^{13}C–H. Method i is both inaccurate and unreliable. Method ii, however, is subjected to severe limitations of accuracy in the case of motional anisotropy and particularly when the details of the model of molecular motion are unknown. In our case the estimation of τ_c is furthermore complicated by the possibility of rotational disorder of the dioxygen moiety[27] and hydrogen bonding between the terminal oxygen atom

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Table I. ^{17}O Chemical Shifts,[a] Line Widths,[b] Chemical Shift Differences ($\Delta\delta$), Ratios of the Line Widths, and NQCCs of Oxygens 1 and 2 of the FeO_2 Moiety of the Compound of Chart I at Various Temperatures

temp/K	δ_2	$(\Delta\nu_{1/2})_2$	δ_1	$(\Delta\nu_{1/2})_1$	$\Delta\delta$	$(\Delta\nu_{1/2})_1/(\Delta\nu_{1/2})_2$	$(NQCC)_1/(NQCC)_2$
307	1755.0	811	2488.3	2584	733.3	3.18	1.78
297	1756.3	890	2487.7	3220	731.4	3.61	1.90
283	1757.9	1399	2484.7	4319	726.8	3.08	1.75
273	1760.5	2017	*c*	*c*			

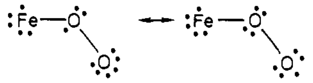
[a] Chemical shifts are reported relative to external 1,4-dioxane with use of the sample replacement technique. Estimated errors from ±1 to ±2.5 ppm, depending on the line width of the resonance. [b] Line widths (Hz) of the resonances at half-height corrected for the line-broadening factors. Estimated error <5% for line widths up to 3 kHz, ~10% for line widths larger than 3 kHz. [c] The breadth of the resonance, ~7 kHz, prohibits accurate estimation of spectral parameters.

and one NH amide group of the handle due to a preferential bent end-on orientation of the oxygen molecule toward two opposite methine bridges.[28,29] By contrast the relative NQCCs can be considered to be more reliable, since they do not depend on τ_c.

From the ratio of the ^{17}O line widths, a NQCC ratio of 1.78 was obtained at 34 °C (Table I), indicating a very important decrease in the NQCC and therefore in the electric field gradient at the oxygen nucleus near the iron atom. It is usually assumed that the largest orbital contribution to the electric field gradient is due to the lone pair MO, followed by the π MO and then by the σ bond MO.[26] Therefore, it can be assumed that electric-field gradient is decreased probably because of the participation of the lone pair of the oxygen 2 into the π system. Although a rigorous interpretation of the relative ratio of NQCCs would require detailed molecular orbital calculations, it is clear that the NQCCs are important structural parameters in addition to the ^{17}O chemical shifts and reveal that the charge distributions about each oxygen atom differ significantly.

By lowering the temperature an increase in the line width is observed (Table I) which is probably due to an increase in the correlation time for molecular tumbling at the site of the superoxo moiety. However, the relative line widths and, therefore, nuclear quadrupole coupling constants of the oxygens 1 and 2 are practically temperature independent. The low-frequency absorption could easily be observed in a wide range of temperatures; however, the broader high-frequency absorption can be observed at low temperatures only by the use of special pulse sequences for acoustic ringing elimination.[14-16]

Electron Distribution in FeO_2 Linkage. Considerable controversy has developed in the last decades concerning the electron distribution on the oxygen bound to metals and particularly whether the FeO_2 moiety should be represented as the $Fe(d^6)O_2$ (low spin) or Fe $(d^5)O_2^-$ unit.[1,2] In the second approach, which was proposed by Weiss,[30,31] an odd number of electrons is assumed on the coordinated dioxygen and is represented by structures III and IV. The unpaired spins of $Fe(d^5)$ and O_2^- are reputedly coupled, thus resulting in the observed diamagnetism of the FeO_2 linkage. This electronic distribution has been inferred from a variety of experimental methods. However, it has recently been reviewed[1] that most of the experimental data can also been explained in terms of bonding models in which the electrons are totally paired.



III IV

According to Goddard and Olafson,[32] the FeO_2 moiety can be represented by an ozone-like structure. There is a σ bond between the Fe and O(2) and a four-electron three-center π bond, which results in a ground singlet state despite the essentially triplet character of the Fe atom and the O_2 moiety. This description of the bound O_2 is consistent with the application of the spin-pairing model of Drago and co-workers[2] to $Fe(d^6)$ adducts of dioxygen. According to Huynh et al.[33] the electronic structure of the FeO_2 linkage can be considered to arise from the interaction of an iron porphyrin moiety and an O_2 molecule with both species in either $S = 0$ or $S = 1$ valence states. The latter, with populations $Fe\{(x^2-y^2)^2(yz)^2(xz)^1(z^2)^1\}$ and $O_2\{(\pi_g^s)^1(\pi_g^a)^1\}$, corresponds to an ozone-like bonding, without net charge-transfer $Fe(d^5)O_2^-$ Weiss-type configuration.[33,34] On bonding, four electrons in the orbitals antisymmetric with respect to the FeO_2 plane (xy on Fe, p_x on O(1) and O(2)) are nearly equally distributed over the three atoms. This is consistent with calculations of the ozone molecule. The iron $3d_{z^2}$ population is considerably less than the ideal value of unity, but the total population in the $4p_z$ and $3d_{z^2}$ orbitals is 0.86, in excellent agreement with the value of 0.87 found for the $2p_z$ orbital of the terminal oxygen in ozone. The total bond order for the O_2 in heme-O_2 is 1.60 and resembles the value of 1.65 for the ozone molecule. For O_2, in the $^3\Sigma_g^-$ and $^1\Delta_g$ electronic configuration, the total order is 2.00 and for O_2^- 1.50.

The analogy between the electronic structure of the FeO_2 moiety and the ozone molecule can be inferred from the ^{17}O NMR data. Solomon et al.[35] reported the ^{17}O chemical shifts of ozone. The bridge oxygen absorbs at 1032 ppm, while the terminal oxygens absorb at 1598 ppm (unfortunately neither details on the solution conditions were given nor line width data). Therefore, the chemical shift difference between the two oxygens is ~566 ppm in reasonable agreement with the value of 733 ppm found for the FeO_2 linkage of the compound of Chart I. It should be emphasized that the terminal oxygens of the ozone molecule absorb at higher frequency relative to the bridge one and this result substantiates furthermore our assignment of the oxygens of the FeO_2 moiety (see discussion on the chemical shifts).

According to Huynh et al.[33] the Weiss-type charge-transfer electronic configuration is at ~1.4 eV above the ground state and the lowest triplet at 1.2 eV. From the ^{17}O data it can be concluded that the energy splitting of the degenerate π orbitals of the oxygen molecule on complexing is of the order 1.04 eV (see our discussion on the chemical shifts). This is in agreement with the work of Huynh et al.[33] but in sharp disagreement with the experimental work of Cerdonio et al.,[36,37] who concluded, on the basis of temperature dependent magnetic susceptibility measurements, that the energy separation between a ground-state singlet and an excited-state triplet is approximately 150 cm^{-1} (Pauling[19] and Savicki et al.[38] have disputed this work).

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(29) An alternative interpretation of the large line width of the terminal oxygen would be an exchange broadening due to hydrogen bonding with one NH amide group of the handle. However, this phenomenon would result in a temperature dependent exchange broadening and therefore temperature dependent ratio of the line widths $(\Delta\nu_{1/2})_1/(\Delta\nu_{1/2})_2$, in contrast to the data of Table I. We are presently investigating the effects of hydrogen bonding on the ^{17}O chemical shifts and line widths of the FeO_2 moiety in a wide variety of synthetic single-face hindered iron porphyrin-dioxygen complexes.

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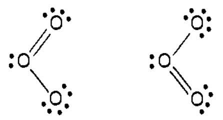
We would like to point out, however, that the analogy between the electronic structure of the FeO_2 moiety and the ozone molecule can be explained on the grounds of totally paired structures.[39,40] According to resonance theory the structure of ozone can be regarded as a hybrid of the forms[40]



Each oxygen atom has four outer electron pairs, either shared or unshared, and each bond can be considered as a hybrid of a single and a double covalent bond. These resonance structures ressemble those of I and II for the FeO_2 moiety. Totally paired structures are also supported by the absence of contact, temperature dependent, paramagnetic chemical shifts (Table I).

Our results clearly indicate that ^{17}O NMR spectroscopy is a highly promising tool in rationalizing the structure, electronic arrangement, and dynamics of the FeO_2 linkage.

Acknowledgment. We thank Dr. M. Marraud (Laboratoire de Chimie-Physique Macromolēculaire, ENSIC-INPL, Nancy) for the access on the Bruker AM-400 spectrometer at the University of Nancy, France, the Research Committee of the University of Ioannina, Greece, and the Institut National de la Santē et de la Recherche Mēdicale (France) for partial finantial support.

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Transition Structures of Ene Reactions of Ethylene and Formaldehyde with Propene

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Abstract: The transition structures for the Alder ene reactions of propene with ethylene to form 1-pentene and of propene with formaldehyde to form 3-buten-1-ol have been located with the STO-3G and 3-21G basis sets. Energetics have been evaluated with the 6-31G* basis set and MP2 correlation energy corrections. Our best estimate of the activation energy (35 kcal/mol) of the propene–ethylene reaction is 14 kcal/mol higher than previous estimates, which were based on the measured activation energy of the reverse process, but it agrees with measured activation energies of similar ene reactions. Although the reaction of formaldehyde has a 5 kcal/mol lower activation energy than the reaction of ethylene, the transition structures of the two reactions are remarkably similar. The details of geometry provided by these calculations assist in the development of interpretations of the stereochemistries of intramolecular ene reactions.

The Alder ene reaction and its reverse, the retro-ene reaction, are common paths of hydrocarbon rearrangement[1,2] and an increasingly useful tool in synthesis.[3-5] Although there have been suggestions about the likely geometry of the transition structure,[1-5] no calculations have been reported for hydrocarbon versions of this reaction. We report here the STO-3G and 3-21G transition structures of the parent Alder ene reaction between propene and ethylene and show how the geometry helps account for some stereochemical aspects of the reaction. A new estimate of the activation energy of the parent reaction is also provided. We have also studied the reaction of propene with formaldehyde and show that although the activation energy is lowered by 5 kcal/mol the transition structure is changed only slightly.

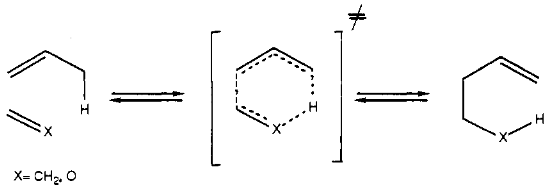

Table I. Energetics of the Ene Reaction of Propene with Ethylene

computational level	activation energy[a]	reaction energy
STO-3G	52.1[a]	−54.2
3-21G	51.7	−23.6
6-31G*//3-21G	61.0	−23.5
MP2/6-31G*//3-21G	31.2	−29.4
experimental	21.4[b] (35)[c]	−28.5
ΔZPE(3-21G)	+0.7	
$\Delta S^{\ddagger}$(3-21G)	−43.0 eu	

[a] The STO-3G and 3-21G total energies of the transition structures are −192.65127 and −193.94254 au, respectively. The reaction energies were calculated with propene and ethylene energies found in: Whiteside, R. A.; Frisch, M. J.; Pople, J. A. *The Carnegie-Mellon Quantum Chemistry Archive*, 3rd ed.; Carnegie-Mellon University: Pittsburgh, PA. 1983. [b] Estimated from the activation energy[8] of 49.9 kcal/mol for the retro-ene reaction of 1-pentene and the heat of reaction[9] of 1-pentene (−11.2 kcal/mol), to form propene (4.88 kcal/mol) and ethylene (12.50 kcal/mol). [c] Estimate of barrier made here (see text).

The transition structures obtained with Pople's GAUSSIAN 80 and 82 programs[6] are shown in Figures 1–4. The calculated energetics are compared to available experimental data in Tables I and II. The exothermicities of both reactions are much too large with the STO-3G basis set,[7a] and consequently, very early transition states are predicted. With the 3-21G basis set,[7b] the reaction energetics are more accurate, and later transition states with more

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(1) The generality of the "ene synthesis" was recognized by Alder in 1943: Alder, K.; Pascher, F.; Schmitz, A. *Berichte* **1943**, *76*, 27. Reviews: (a) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. (b) Keung, E. C.; Alper, H. *J. Chem. Educ.* **1972**, *49*, 97. (c) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (d) Roth, W. R. *Chimia* **1966**, *20*, 229.

(2) Gajewski, J. J. *Hydrocarbon Thermal Isomerizations*; Academic: New York, 1981.

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