The data in Fig. 1 indicate that there was an about fourteenfold stimulation of cholesterol synthesis by 20 mM citrate and a fourfold stimulation by 20 mM α-ketoglutarate. Under the same conditions, pyruvate, isocitrate, succinate, fumarate, or malate had little effect on the cholesterol synthesis. On the activity level of the control experiments (*ca.* 80 counts/20 min) the incorporation of acetate into cholesterol was 5×10^{-4} %. This low activity may be related to the fact that our incubation medium contained neither ATP nor NADPH.

Some results of the earlier studies [2,3] are not consistent with our results, but the discrepancy may be due to the different material and to the considerably higher concentration of citrate we used. Our new and unexpected results suggest that the regulating action of citrate and α-ketoglutarate on cholesterol synthesis may be more complex also in physiological conditions.

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Comments on Some Contradictory Results of Polarimetric and NMR Studies of the Configurational Inversion of Several Biphenyl Derivatives

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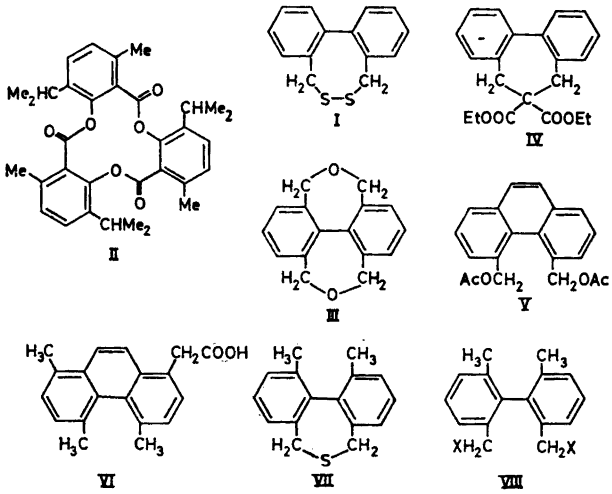
There are apparently very few examples in the literature of suitable optically active molecules whose configurational inversion process has been studied by both polarimetric and NMR kinetic methods. Lüttringhaus and Rosenbaum [1] investigated 4,5-6,7-dibenzo-1,2-dithia-cyclooctadiene (I) by both methods, but were unable to obtain a rate constant with NMR since the large enthalpy of activation ($\Delta H^{\ddagger} = 26.6$ kcal/mole by polarimetry) made the molecule inappropriate for study on the NMR time scale.

Ollis and Sutherland [2] studied the temperature dependence of the NMR spectrum of tri-*o*-thymotide (II) and compared their results with those available from an earlier polarimetric investigation by Newman and Powell.[3] However, the paper by Ollis and Sutherland [2] is in the form of a preliminary communication, and it is stated that "...it has yet to be established that the exchange process and the racemization process involve the same conformational changes." [2]

Ōki and Iwamura [4] have recently reported a NMR kinetic study of the AB system provided by the $-CH_2-$ protons of the dioxepin III, using line width measurements to estimate the rate of exchange of proton environments both above and below the coalescence temperature. Their activation parameters are in agreement with those obtained polarimetrically (from kinetic data at two temperatures) by Mislow *et al.*[5]

Other data from the literature may be combined to yield some strikingly anomalous and contradictory conclusions about the optical stability of several biphenyl derivatives and related compounds. An example is afforded by a comparison of the results of Iffland and Siegel [6] (polari-



metric) with those of Sutherland and Ramsay [7] (NMR) on the rate of inversion of the bridged biphenyl diester IV. The former authors report a half life of 80 min in cyclohexane solution at 305.7°K, whereas a half life of *ca.* 10^{-3} sec in pyridine solution at the same temperature may be estimated from the $\Delta G_c^{\ddagger}$ value given by the latter authors. These mutually contradictory results have been previously pointed out and discussed by Hall and Poole,[8] who suggest that the change from multiplet to singlet in the NMR spectrum of IV "may have some explanation other than that of a very rapid inversion."

The use of approximative formulae such as those derived by Gutowsky and Holm [9] or Rogers and Woodbrey [10] for the determination of kinetic parameters from NMR spectra at various temperatures is well known to lead to systematic errors in some cases, and caution in the use of these approximations has been urged by several authors.*,[11] At the coalescence temperature (T_c), the approximate Gutowsky-Holm equation [9] $k_c = \pi(\delta\nu)/\sqrt{2}$ for the uncoupled AB case and the equation derived [12] from the treatment of Alexander,[13] $k_c = \pi[(\delta\nu)^2 + 6J_{AB}^2]^{1/2}/\sqrt{2}$ for the mutually coupled AB case, give good values for k_c, the exchange rate constant at T_c, from which a value for the free energy of activation ($\Delta G_c^{\ddagger}$) may be calculated *via* the Eyring equation [14] with a probable error of about ± 0.2 kcal/mole. The most reliable activation parameters for a given system from NMR kinetic data are obtainable only by carrying out a complete line shape analysis at various temperatures with the aid of a computer, using the semi-classical approach of Gutowsky and Holm [9] as modified by McConnell,[15] or the quantum mechanical density matrix approach developed by Alexander.[13]

In spite of complete line shape analyses, including the variation of the relaxation time T_2 and chemical shift parameter $\delta\nu$ as functions of the temperature, results have been reported for several compounds which are impossible to reconcile with independent polarimetric data for similar molecules. A case in point is 4,5-*bis*-(acetoxymethyl)-phenanthrene (V) which was recently reported by Munday and Sutherland [16] to have an inversion rate constant of 0.32 sec^{-1} at 297.8°K in nitrobenzene-d_5 solution. This may be compared with a polarimetric value of the order of 10^{-5} sec^{-1} at 298°K for the 4,5-dimethylphenanthrene derivative VI in chloroform solution, estimated from the work of Newman and Hussey.[17] There is thus a difference in rate by a factor of 10^4 between these two molecules which, as pointed out by Munday and Sutherland,[16] cannot be fully explained in terms of a solvent effect on the inversion rate, the difference in size of methyl and acetoxy-

* Prof. Sture Forsén and Mr. K.-I. Dahlqvist, personal communication to R. E. C.

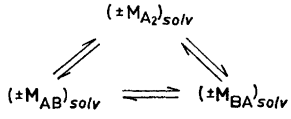
methyl groups and/or the presence of substituents in the 1- and 8-positions of VI.

The importance of the choice of solvent for the appearance of magnetic nonequivalence in diastereotopic [18] protons is well-illustrated by two examples from the comprehensive work of Mislow *et al.*,[5] who found that i) the $-CH_2-$ protons of the dimethylthiepin VII gave a sharp singlet in five solvents (CCl_4, CS_2, $CDCl_3$, C_5H_5N, $C_6H_5NO_2$) but an AB pattern in benzene; and ii) the resonance of the $-CH_2-$ protons of 6,6′-dimethyl-2,2′-*bis*(bromomethyl)biphenyl (VIII, X = Br) remained a singlet even at 100 MHz in six different solvents, including benzene, nitrobenzene, and 1-chloronaphthalene, whereas for the corresponding diol (VIII, X = OH) an AB pattern was observed. All three of these compounds are known to possess high optical stability.[5]

The process of configurational inversion which is observed polarimetrically interchanges the environments of all pairs of diastereotopic protons (or groups of protons) in a molecule. In the case of an optically active molecule M in which one pair of protons, A and B, is diastereotopic we may write

$$\pm M_{AB} \underset{}{\overset{k_{inv}}{\rightleftharpoons}} \pm M_{BA} \qquad (1)$$

where the change in subscript from AB to BA indicates the exchange of proton environments, and k_{inv} is the rate constant for inversion. The process observed with the NMR method is the loss of magnetic nonequivalence of the diastereotopic protons. Rapid configurational inversion is *one* way in which this may be brought about, but *it is not the only possible path to magnetic equivalence*. The occurrence of so called "collision complexes" between solvent and solute in which the solvent molecules are oriented in a non-random fashion with respect to the solute molecule is well-documented,[19] especially when the solvent as well as the solute are aromatic. It is thus not unreasonable to suggest that the AB protons in our hypothetical molecule might either gain or lose magnetic nonequivalence *via* solute-solvent interactions, *without configurational inversion:*



In this scheme, $\pm M_{A_2}$ represents a molecule in which the diastereotopic protons have become (accidentally) magnetically equivalent, and *solv* denotes the solvent molecules that take part in the "collision complex". The changes indicated by the arrows are considered to occur as the result of some reorientation of the solvating molecules within a solute-solvent complex.

Thus, while the rate observed polarimetrically is unambiguously related to the rate of inversion, the rate constant obtained from NMR kinetic data may be composite and represent several inseparable processes, including the inversion reaction. It is obvious from these considerations that comparisons of NMR rate constants with those obtained from polarimetric data for the same molecule must be made with the utmost caution. Furthermore, comparisons of rate constants determined by the NMR method for molecules such as those discussed here may be misleading if differences in solvation are likely to be significant.

Experiments designed to investigate the suggestions presented in this communication are in progress.

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N-Alkoxythiocarbamoylimidazoles

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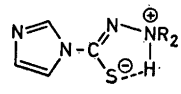
As part of a study of the thiocarbazoyl group [1] we became interested in the title compounds, which might function as precursors for the very unstable alkoxyl isothiocyanates (*N*-thiocarbonylalkoxyamines) [2] in analogy with the conversion of *N*-thiocarbazoylimidazoles to *N*-isothiocyanatoamines.[3] Staab and Walther [4] have prepared *N*-benzyloxythiocarbamoylimidazole and shown that only its cyclohexylammonium salt is formed on attempted aminolysis with cyclohexylamine.

The reaction between *N*,*N*-thiocarbonyldiimidazole (I) and methoxyamine (IIa), ethoxyamine (IIb), or butoxyamine (IIc) proceeds readily at room temperature to give imidazolium salts of *N*-alkoxythiocarbamoylimidazoles (IIIa–IIIc). Removal of imidazole from IIIa was effected by dissolving it in boiling acetone: *N*-methoxythiocarbamoylimidazole (IVa) precipitated in quantitative yield. Decomposition of IIIb or IIIc in an analogous way failed, probably because the products are soluble in acetone and the equilibrium accordingly is not displaced to the right.

The infrared and NMR spectra (in KBr and $CDCl_3$, respectively, except where otherwise stated) support the structures assigned to III and IV. In the NMR spectra of IIIa and IVa the CH_3–O singlets are observed at $\tau = 6.18$ ppm which indicates that the methoxythiocarbamoyl group is in the same state in both compounds. The imidazolium ion in IIIa gives rise to three signals at $\tau = 2.95$, 2.12, and *ca.* −4.2 ppm (ratio 2:1:2). The two former signals are displaced to $\tau = 2.76$ and 1.52 ppm in D_2O close to the positions ($\tau = 2.70$ and 1.55 ppm) observed for imidazolium chloride in D_2O. In addition, IIIa displays three partly resolved triplets with equal areas at $\tau = 3.04$, 2.27, and 1.30 ppm arising from the unprotonated imidazolyl group. As expected for the dipolar structure depicted for IVa the three corresponding peaks are observed at $\tau = 2.91$, 2.18, and 1.04 ppm, which indicates a deshielding of the C–H protons of the imidazole ring relative to the anion of IIIa. The signal from the NH^+ proton in IVa is observed at $\tau = -1.05$ ppm; comparison with the above τ-value for the imidazolium ion points to the occurrence of inter- or intramolecular hydrogen bonding in IVa. The NMR spectra of IIIb and IIIc introduce no new features except the further signals arising from the alkyl groups.

The most important diagnostic feature of the infrared spectra of IIIa and IVa is the occurrence of intense absorption characteristic of the hydrogen-bonded imidazolium group in th range between 2500 and 3200 cm^{-1}.[5] In contrast the spectra of 1-(*N*,*N*-dialkylthiocarbazoyl)-imidazoles,[1] which have the dipolar struc-



V