studies in physical and theoretical chemistry 37

TOPICS IN MOLECULAR INTERACTIONS

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Reprinted from Proceedings of the Indian Academy of Sciences (Chemical Sciences),
Vol. 94, Nos 1 & 2, Indian Academy of Sciences, Bangalore, India

ELSEVIER SCIENCE PUBLISHERS
Molenwerf 1
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

Distributors for the United States and Canada:

ELSEVIER SCIENCE PUBLISHING COMPANY, INC.
52, Vanderbilt Avenue
New York, NY 10017

Library of Congress Cataloging in Publication Data
Main entry under title:

Topics in molecular interactions.

(Studies in physical and theoretical chemistry; 37)
'Reprinted from Proceedings of the Indian Academy of Sciences (Chemical Sciences), vol. 94 nos. 1 & 2, Indian Academy of Sciences, Bangalore, India.'
Bibliography: p.
Includes index.
1. Molecular dynamics—Addresses, essays, lectures
I. Orville-Thomas, W. J., 1921– II Ratajczak, H
III. Rao, C. N. R. (Chintamani Nagesa Ramachandra), 1934– . IV. Indian Academy of Sciences
V. Series: Studies in physical and theoretical

chemistry; v. 37.
QD461.T67 1985 541.2'2 85–10309

ISBN 0–444–99556–0 (Vol. 37)
ISBN 0–444–41699–4 (Series)

Printed in India.

studies in physical and theoretical chemistry

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Preface

At present the field of intermolecular interactions, or to use the current phrase 'molecular interactions', is one of the major areas of molecular science. One reason for this is that the topic is important in chemistry, physics, and biology, and even more so at the interfaces of these subjects.

This volume deals with a variety of problems. These fall into two groups. The first contains important topics which have not recently been dealt with in an authorative fashion, such as the information given by studying hindered internal rotation. This group also includes treatments of the crystal and glassy states which are, to some extent, complementary.

The second group contains contributions based largely on nuclear magnetic resonance work. Nuclear spin relaxation studies have led to intimate knowledge concerning association effects. The approach developed principally at the Karlsruhe laboratory is described. Also included is a second experimental chapter devoted to the way in which light scattering studies provide information on multipole forces in molecular interactions. Other topics based on NMR studies show how this technique yields valuable information on molecular and ion-molecule interactions.

It is a great pleasure for the Editors to thank all the authors who have contributed to this substantial publication.

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CONTENTS

Hindered internal rotation and intermolecular interactions

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1. Introduction

Flexibility of chemical bonds is one of the important factors that determine the properties and reactivity of a molecule. Most chemical bonds, while not completely rigid, still are not involved in totally free rotation. With the development of various physical methods of investigation, it has become evident that the internal rotation about a bond is hindered to varying degrees. The earlier investigations of internal rotation mainly used the methods of dipole moments and Raman and infrared spectroscopy, and the results are summarized in an excellent monograph written by Mizushima (1954).

Hindered internal rotation at ambient temperatures was first detected by means of nuclear magnetic resonance (NMR) in N,N-dimethylformamide (DMF) in the middle of the nineteen-fifties by Phillips (1955) and Gutowsky and Holm (1956). It was observed that the bandshape of the NMR spectrum of DMF was modified, depending on the rate at which the two methyl groups exchanged sites. The resulting bandshapes were then analysed based on the modified Bloch equations (Gutowsky and Saika 1953; Gutowsky and Holm 1956) to yield the rate of the exchange. Subsequent to these original works, a large number of bandshape studies have been reported on amides. The special attention given to this class of compounds may be attributed partly to the fact that the dynamic process for the carbon-nitrogen bonds in amides as detected by NMR usually takes place at an easily accessible temperature range (the barrier to rotation being around 50 to 90 kJ/mol), and also partly to the importance of the amide linkage in peptides and proteins.

Determination of smaller energy barriers has been made possible by improvement in the variable temperature equipment, by the use of nuclei other than protons, and/or by the introduction of higher magnetic field strengths and pulse and FT methods. At the same time, the bandshape calculation has become much more precise for coupled spin systems with the introduction of a quantum mechanical approach using the density matrix procedure (Kaplan 1958a, b; Alexander 1962a, b).

Complete bandshape analysis has now been well established and comprises the principal method of the branch of NMR called dynamic nuclear magnetic resonance (DNMR). Other methods include the use of relaxation times and the double resonance technique, which are especially valuable in obtaining information about those dynamic properties of the system which occur at rates too fast or too slow for the application of bandshape methods, even though the interpretation of the data is rather complex. A great variety of rate processes are now being reported including hindered internal rotation about single and double bonds, ring reversal processes, nitrogen inversion and other intra- and intermolecular exchanges.

In many of these studies, the observed thermodynamic data are explained in terms of the effects of substitutents and steric hindrance on internal rotation, as well as the effect of molecular interactions. Compared with the former two effects, the effect of molecular interactions on internal rotation has not been well understood, due partly to the small size of the effect and also to the complexity of the interpretation which has to take into account the microscopic environment of the rotational isomers in solutions. Nevertheless, a few measurements in the gaseous state as well as theoretical calculations using molecular orbital or force field methods have indicated that a significant difference may exist in the barriers to internal rotation in liquid state as compared to gas. In view of the fact that most of the measurements are made in solutions, it is essential to obtain a much greater knowledge of the effect of solvation and molecular associations on the rate of hindered internal rotations.

Excellent reviews are available on DNMR studies of internal rotations: Binsch (1968), Kessler (1970), Stewart and Siddall (1970), and Sutherland (1971) dealt thoroughly with the studies up until 1969 in their reviews. 'Internal Rotation in Molecules' edited by Orville-Thomas (1974) discusses the studies made by various physical methods including DNMR. Further, in 1975, Jackman and Cotton (1975) edited an extensive review book, 'Dynamic Nuclear Magnetic Resonance Spectroscopy', which describes in detail the theories, methods and application of DNMR and contains all the main studies reported up to 1974.

Thus this article will present selected examples of more recent studies on hindered internal rotation which appeared mainly from 1974 to 1983. Since the attention is to be focussed on the effect of molecular interactions, it will not be an exhaustive article covering all the main studies. Examples chosen will also be dependent on personal interest and availability. Results reported in literature on the carefully determined values of activation enthalpies ($\Delta H^{\neq}$) and entropies ($\Delta S^{\neq}$) have been included to the greatest extent possible despite the reputed uncertainty in these parameters as compared with free energy of activation ($\Delta G^{\neq}$) values, though, unfortunately, a large number of studies list $\Delta G^{\neq}$ values only. Due to limited space, no works on metal compounds are included, neither are the DNMR works on ring reversals or nitrogen inversion except for a few examples. SI units are used throughout the text; the conversion factor of 4·184 J/cal has been applied to the published thermodynamic data where necessary.

2. Methods of measurement

Since excellent treaties have been published recently on practical aspects of DNMR (Binsch 1975; Kaplan and Fraenkel 1980; Sandström 1982), only a few points will be selected and discussed here.

2.1 *Complete bandshape analysis*

The method of calculating nuclear magnetic resonance bandshapes in the presence of chemical exchange processes was first presented by Gutowsky *et al* (1953) as a direct modification of the Bloch equations to incorporate the effect of exchange. This 'classical' bandshape method for the uncoupled two-site exchange model and its various extensions such as to N-site models and weakly coupled systems have been applied to many systems and have served greatly in the understanding of intramolecular and intermolecular exchange processes. Various approximate procedures have been devised for slow, intermediate and fast exchange cases so that the rates may be obtained readily based on a single-parameter taken from the observed spectrum. Despite large errors often involved in these single-parameter approximations (Allerhand *et al* 1966; Kost *et al* 1971; Berg *et al* 1977), they have been quite frequently used.

Since the Bloch equations are derived for an ensemble of independent spins, the modified Bloch equations are also only applicable to uncoupled spin systems. Strongly coupled systems require a full quantum mechanical treatment in terms of a density matrix. Such a density-matrix method of bandshape calculations has also been well established and presented in forms suitable for computer calculations. See, for example, Binsch (1975) for a list of computer programs. Recent additions to the list include DNMR 3-IT2 (Musso *et al* 1978) and DNMR 5 (Stephenson and Binsch 1978) which incorporate least square iterative simulations.

Now that the theory and method of the complete bandshape calculation have been established and also efficient digital computers have become readily available for the calculations, this method is performed almost routinely in many laboratories. This is a welcome situation for the study of molecular interactions in this field, because the interaction energy is rather small compared to the energy barriers for internal rotations, sometimes within the margin of error limit of measurements, and thus the results may be significantly influenced by the accuracy of measurements. Furthermore, it has also been pointed out that such thermodynamic parameters as $\Delta H^{\neq}$ and $\Delta S^{\neq}$, which are notoriously susceptible to systematic errors, contain relatively more information concerning molecular interactions, as compared to relatively error-free $\Delta G^{\neq}$, the free energy of activation. Accordingly, accurate measurements are required to study the effect of molecular interactions.

Application of the bandshape analysis to obtain activation parameters involves; (a) obtaining mechanically undistorted spectral lines at a wide range of accurately measured temperatures, (b) simulating the obtained bandshape by calculating the theoretical line for the correct spin system and using accurately determined input parameters such as the population p, the spin-spin relaxation times T_2, and the relative chemical shifts in the absence of exchange $\Delta\nu$, for the nuclei at each site, and (c) determining thermodynamic parameters from the temperature dependence of the statistically weighted rate data through Arrhenius' and Eyring's equations. This procedure, when carefully followed, is considered to give the most accurate rate constants and activation parameters for molecular rotations at present. Probable errors and means to minimize them in each of these steps are discussed in the reviews by Binsch (1968, 1975) and Szymanski *et al* (1977) and also in numerous articles, so only a few points will be mentioned here.

Narrow temperature ranges of study and uncertainty in temperature measurement are often listed as the primary sources of errors in bandshape studies. The conventional methods for measuring the sample temperature include inserting in the sample-holding space, (a) a thermocouple or thermister, or (b) an 'NMR thermometer' such as a tube or capillary containing methanol or ethylene glycol, under identical conditions to those used for the spectral measurement, and recording the emf or the chemical shift, both immediately before and after the bandshape measurement at each temperature. In the case of (b), the chemical shift of the strongly temperature dependent signals of these compounds should be precalibrated by the method of (a). Calibration data are also available in the literature (Van Geet 1968, 1970; Raiford *et al* 1979). In addition to the measurement of the correct temperature, it is also important to control it accurately, minimize the temperature gradient along the sample tube and avoid refluxing of the solution inside the tube, especially when it is vacuum-sealed.

A source of error which is often overlooked or not correctly accounted for is the inherent temperature dependence of the bandshape parameters such as $\Delta\nu$, p and T_2. This phenomenon is particularly marked in those systems where molecular association is considered to be significant. Usually, a linear dependence of these parameters on temperature is assumed, and the kinetically unaffected part of the linear plots is extrapolated to the coalescence region to obtain the necessary values. Nonlinear dependence has also been observed (Hólik and Mannschreck 1979).

Neglect of small long-range spin-spin couplings has been sited as a potentially important source of systematic errors in the bandshape analysis. The effect could be particularly evident on the values of $\Delta H^{\neq}$ and $\Delta S^{\neq}$ (Drakenberg and Carter 1975). When dimethylacetamide was treated as an $A \rightleftharpoons B$ exchange system instead of $AX_3 \rightleftharpoons BX_3$ system which explicitly includes the five-bond long-range proton-proton coupling, the above authors showed that $\Delta H^{\neq}$ was different by about 10%, while $\Delta S^{\neq}$ was six times too large, demonstrating that a spurious 'entropy effect' can easily arise from neglect of unresolved long range couplings.

The accuracy of the measurement may be improved by deliberately selecting complex spin systems (Höfner *et al* 1978a, b). Similarly, the bandshapes of different groups or of multiple types of nuclei within a molecule may be studied to provide cross-checks on the result of a single rate process. If relaxation time measurement is conducted in conjunction with the bandshape study, a much wider temperature range may be studied to increase the accuracy (Bovée 1979).

^{13}C DNMR with broadband proton decoupling has been gaining popularity recently, because of the very simple non-spin coupled spectra (which may be easily analysed by means of modified Bloch equations) and also because of the large chemical shift difference between the exchanging carbon signals. The large chemical shift difference between the exchanging carbons offers a wider temperature range to study especially when used in conjunction with ^{1}H DNMR, as well as allowing the measurement of lower barriers (fast rate processes). ^{13}C DNMR studies have been reviewed by Mann (1977b).

Large chemical shift differences are also commonly observed in ^{19}F spectra, but strong couplings between the fluorine atoms or with protons often give rise to more complex spectra. Such complexity has been utilized for added accuracy (Jost *et al* 1979). The prospect of and the problems involved in ^{15}N DNMR have been discussed by Roberts (1979).

^{1}H DNMR has been investigated in liquid crystalline samples (Schmiedel *et al* 1980) and in samples oriented in nematic solvents (Khetrapal and Kunwar 1982).

2.2 *Other methods*

2.2a. *Methods of relaxation times*: While complete bandshape analysis has been established as a standard tool for the investigation of internal rotation of molecules, its application is generally limited to processes with rates of 10^0–10^5 sec^{-1}. Important intramolecular motions such as methyl rotation and segmental motions along chainlike molecules occur at a much faster rate, which may be studied by NMR techniques in terms of other important parameters, relaxation times. The range of measurable rates will then be extended in both directions to 10^{-2}–10^{11} sec^{-1}. The theory and practical methods of application to exchange problems are discussed by Reeves (1975), Freeman and Hill (1975), and Sandström (1982).

Various techniques for the measurement of T_1, the spin-lattice relaxation time, have been described and their accuracy compared by Weiss and his coworkers (Weiss *et al* 1980; Becker *et al* 1980). The spin-lattice relaxation time of nuclei may be represented by the expression,

$$1/T_1 = 1/T_{\mathrm{DD}} + 1/T_{\mathrm{SR}} + 1/T_{\mathrm{Q}} + 1/T_{\mathrm{other}},$$

where T_{DD} is the dipole-dipole contribution to the relaxation, T_{SR} the spin-rotation contribution, T_{Q} the contribution due to quadrupolar effect, and $1/T_{\mathrm{other}}$ the contribution from all other types of relaxation. The relative importance of these contributions depends on the nuclei and the molecular system to be studied. The most important relaxation mechanisms for nuclei of spin = 1/2 in the liquid phase are intra- and inter-molecular dipole-dipole (DD) interaction and spin-rotation (SR) contribution, while for those nuclei with spins $\geqslant 1$ a quadrupolar (Q) contribution is the predominant mechanism of relaxation.

In order to apply the available theory of relaxation and so obtain the desired information about the exchange processes from the experimental relaxation data, it is necessary to separate the data into each contributing mechanism. For protons, this is not easy in many cases because inter- and intramolecular dipole-dipole and the spin-rotation contributions are of comparable sizes and not easily separable. In favourable cases of small molecules, the separation has been accomplished by making full use of information obtained from the relaxation measurements of other nuclei in the same molecule (Suchanski and Canepa 1979). For larger and more complex molecules, measurement of multi-selective proton spin-lattice relaxation rates has been proposed as a useful technique in studies of the internal motions (Niccolai and Tiezzi 1979; Niccolai *et al* 1980).

On the other hand, the case of ^{13}C atoms directly bonded to protons has the advantage that the DD interaction is dominated by the carbon-proton dipolar interaction only (Kuhlman *et al* 1970), the amount of which can be estimated by observing the carbon-proton nuclear Overhauser enhancement (NOE) effect. The dipolar contribution to T_1 may thus be calculated and separated from the spin-rotation contribution. The obtained T_{DD} to which the intermolecular contribution is usually negligible is then interpreted to extract exchange rate according to the method developed by Woessner (1961, 1962), Woessner *et al* (1969). This treatment is particularly suited for the study of methyl group rotation. The temperature dependence of T_{DD} will then provide the thermodynamic activation parameters (Erickson *et al* 1980).

The spin-rotation relaxation time, T_{SR}, has also been found to yield the barrier to methyl group rotation. The contribution of T_{SR} has been obtained from the ^{13}CT_1 and the NOE factors and related to the potential barrier of a methyl group (Zens and Ellis 1975; Tancredo *et al* 1978).

Information on the exchange rates may be obtained from the spin-spin relaxation time, T_2, too. The T_2 value for a system of two exchanging spins A and B measured by the spin-echo technique of Hahn or the Carr-Purcell (-Meiboom-Gill) pulse sequence is a function of the relative chemical shift $\Delta\nu_{AB}$, the lifetime τ_A and τ_B, and the transverse relaxation times at each exchange site, T_2^A and T_2^B (Luz and Meiboom 1963). The theory and the method have been described by Freeman and Hill (1975) and by Jen (1978), though not many applications have been reported.

2.2b. *Saturation transfer*: The application of double resonance for the study of chemical exchange rates was first proposed by Forsén and Hoffman (1963, 1964) and is called the saturation transfer method. In the case of a two-site exchange, for example, the size of the signal at one site is measured in the absence and the presence of a strong rf field at the second site, and the resulting intensity perturbations at the first site are studied. This method is applicable to slow exchange processes where the rates are of the order of 10^{-2} to 10^{-1} $\sec^{-1}$ and, if used together with bandshape analysis, may provide a powerful method of determining accurate activation parameters (Mann 1977a).

2.2c. *Relaxation time coalescence*: Another method which may be used to obtain information about the exchange rate in the slow motional range has been proposed by Lambert and Keepers (1980). They made a detailed analysis of the temperature dependence of non-selective ^{13}C spin-lattice relaxation times (T_1^A and T_1^B) for the N-methyl carbons, *A* and *B*, of N,N-dimethylformamide (DMF) and found the observed T_1^A to show a peculiar sigmoidal behaviour as the temperature is changed. This was explained as being due to a superposition of exchange effects on dipole-dipole relaxation. Regression analysis using a double-exponential expression yielded the rotational rate ($k = 1/\tau$) about the amide bond and the true relaxation times. The method is especially suitable for studies on exchange processes with high barriers since the effects of exchange on relaxation times were most marked at a temperature range below that where any lineshape change occurred.

2.2d. *Equilibration method*: When the exchange process is between non-identical isomers, rate of return to the equilibrium from a non-equilibrium condition will provide the rate constant for the exchange. This method is especially useful when a relatively large energy difference between the ground states of the isomers causes the population of the high-energy species to be too small to be studied by the bandshape method.

The system may be put into an initial non-equilibrium state by a number of means; a pure isomer may be produced by synthesis (Mannschreck *et al* 1967) or one of the isomers may be preferentially complexed and concentrated (Gutowsky *et al* 1967) at a temperature where the exchange rate is small enough. The NMR spectra are then studied as the mixture is brought to an equilibrium at a higher temperature. Anet and Squillacote (1975) demonstrated that a relatively high concentration of the minority form of N-methylformamide (*cis*) present at a high temperature (813 K) could be frozen out by depositing the mixture instantaneously to a surface of a very low temperature (208 K) to trap the high-temperature equilibrium ratio, and the rate was studied through the change in the peak intensities as the mixture was brought to equilibrium at the low temperature.

2.2e. *Two-dimensional (2D)* DNMR: The application of two-dimensional ^{13}C DNMR for chemically exchanging systems has been proposed by Ernst and his coworkers (Jeener *et al* 1979; Huang *et al* 1981).

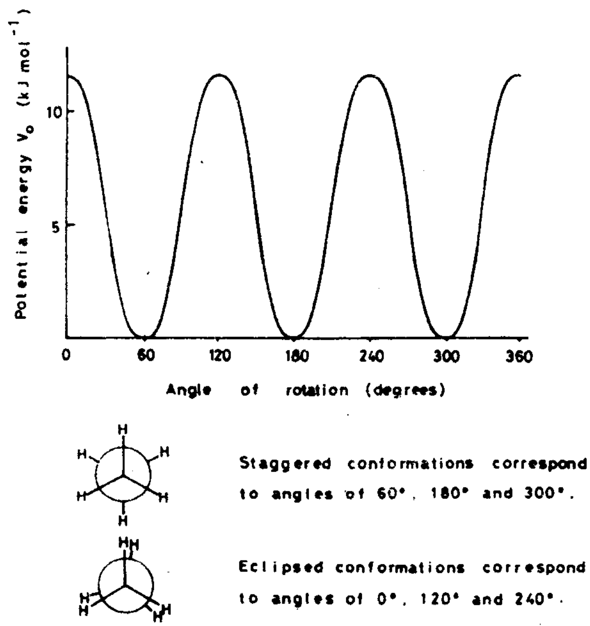
3. Hindered internal rotation about various bonds

3.1 *Carbon-carbon bond*

3.1a. *Substituted ethanes* (sp^3–sp^3): The barriers hindering internal rotation around single bonds in molecules are normally small. In ethane, the simplest molecule for which rotation around a carbon (sp^3)-carbon (sp^3) single bond is possible, the barrier to rotation is known to be of the order of $12\ \mathrm{kJ\,mol^{-1}}$ (Weiss and Leroi 1968). The potential energy of the molecule varies with the angle of rotation as shown in figure 1. The barrier to internal rotation measures the difference in energy between the staggered ground state and eclipsed transition state.

The origin of the barrier to internal rotation in ethane has been the subject of many theoretical discussions. Quantum mechanical calculations have shown that the main part of this barrier is caused by the orthogonality of the molecular orbitals that is required by the Pauli principle (Christiansen and Palke 1977; Morokuma and Umeyama 1977). Contributions from bond-antibond interactions have also been suggested as a possible primary contribution to the barriers from the result of an INDO calculation (Brunck and Weinhold 1979). When the two methyl groups are separated by three bonds, as in 2-butyne, CH_3–C≡C–CH_3, the barrier to rotation becomes negligibly small, almost a thousand-fold; a microwave determination gives a barrier of less than $12\ \mathrm{J\,mol^{-1}}$ for the closely related molecule, methylsilylacetylene (Kirchoff and Lide 1965), and an *ab initio* calculation estimates it to be 20–$25\ \mathrm{J\,mol^{-1}}$ (Radom and Pople 1970).

In addition to this intrinsic barrier found in ethane, contributions from steric and electrostatic attractive and repulsive interactions become important in determining the



Staggered conformations correspond to angles of 60°, 180° and 300°.

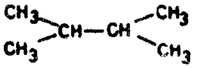
Eclipsed conformations correspond to angles of 0°, 120° and 240°.

Figure 1. Potential energy as a function of rotational angle for ethane.

rotational barrier and conformational equilibria when ethane is substituted with various groups. This subject has been studied extensively by NMR and other techniques, and the experimental and theoretical results obtained before 1974 are included in a number of reviews (Binsch 1968; Kessler 1970; Sutherland 1971; Abraham and Bretschneider 1974; Sternhell 1975). It is only recently, however, that application of complete bandshape analysis became popular in the DNMR study of substituted ethanes. The extremely low temperatures required to slow down the rotation about single bonds with small barriers, as well as frequent isochrony of the chemical shifts of exchanging protons have been the main difficulties. Table 1 lists the barriers to C–C bond rotation that have recently been measured in substituted ethanes.

It has generally been observed earlier (Sternhell 1975) that in halogenated ethanes the barriers are dependent on the steric bulk of halogens, as well as the total number of the halogen atoms. In the case of alkyl substituents, an increase in the barrier with the group size is also evident, indicating that steric repulsions and electrostatic repulsive forces between the bonds of similar polarity are the important factors determining the barrier heights (Anderson *et al* 1976).

When there are two possible pathways for rotation with different barrier heights, the process with the lower energy barrier is found to take place exclusively. Lunazzi *et al* (1977a) employed 90·5 MHz ^{13}C NMR to study the *trans-gauche* interconversion in 2,3-dimethylbutane **1**. The two pathways are the *gauche-trans-gauche* process and the *trans-gauche-gauche* process. In a *gauche-trans* transition state, only one pair of methyl groups is eclipsed at a time, while in a *gauche-gauche* transition state, two pairs become eclipsed simultaneously. From the low temperature (173–93 K) bandshape analysis of the methine signal, together with an *ab initio* SCF-MO calculation, they concluded that the interconversion takes place exclusively via the *gauche-trans-gauche* process, with a free energy of activation of 18 kJ mol^{-1}. The calculation predicted that the *gauche-gauche* barrier would be about 33·5 kJ mol^{-1}.



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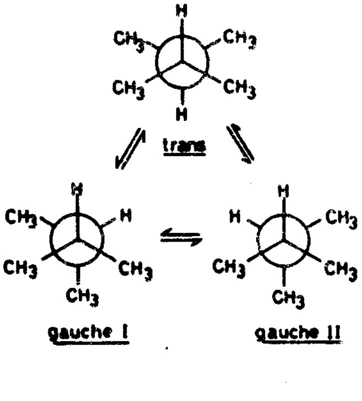
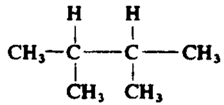
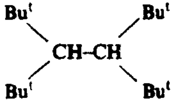
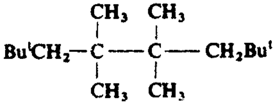
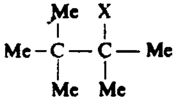


Table 1. Barriers to internal rotation in substituted ethanes and propanes[a].

No.	Compound	Substituent	Solvent[c]	T(K)[b]	$\Delta G_T^{\neq}$	$\Delta H^{\neq}$	$\Delta S^{\neq}$	Reference
1.			CHF_2Cl/ CH_2FCl	93	18·0			1
2.			HCB/ DMSO-d_6	413	96			2
3.			CHF_2Cl	254·5	57·7			3
4.		X = H	$CHFCl_2$	143·4	29·2			3
		X = F	CH_2Cl_2	149·8	33·6	41·4	51·0	4
		X = Cl	$CHFCl_2$	216·6	43·6	37·2	−29·7	3
		X = Br	$CHFCl_2$	214·2	44·9	43·4	−2·1	3
		X = I	CH_2Cl_2	206·9	46·6	49·9	16·7	3
		X = C≡N	CF_2Cl_2	170·0	36·4			5
		X = CHO	CF_2Cl_2	154·5	32·6			5
		X = COOH	CF_2Cl_2	152·1	32·6			5