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Electron Paramagnetic Resonance Study of Inversion Barriers and Conformations in Substituted Cyclopentyl Radicals

Roger V. Lloyd*[1a] and David E. Wood[1b]

Contribution from the Departments of Chemistry, Memphis State University, Memphis, Tennessee 38152, and University of Connecticut, Storrs, Connecticut 06268.
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Abstract: The cyclopentyl (I), methylcyclopentyl (II), fluoromethylcyclopentyl (III), chloromethylcyclopentyl (IV), and isocyanatocyclopentyl (V) radicals have been prepared by x-irradiation of the substituted cyclopentane in adamantane. By computer analysis of the temperature dependences of the line widths in their EPR spectra, the activation energies for interchange of the ring β protons were obtained and conclusions were drawn about the lowest energy geometry and the mode of inversion for each radical. The activation energies are (kcal/mol): radical I, 1.3; II, 3.2; III, 2.4; IV, 5.3; V, 1.9.

I. Introduction

There has been a long-standing interest in the study of dynamic processes in alicyclic molecules and a vast literature has developed concerning the application of NMR techniques to the determination of conformations and inversion barriers in such systems.[2] The use of EPR for similar investigations in cyclic radicals is much less common, however, even though the same information can be learned about their structures and conformational preferences. Much of the present knowledge is based on the results of organic reaction studies, which do not directly probe radical intermediates.[3a] EPR has been mostly used to examine six-membered rings, such as the cyclohexyl radical for which an activation energy for chair-to-chair inversion has been obtained by the analysis of the temperature dependence of line widths.[3b,4,5]

The dynamics of five-membered rings are considerably more complicated than for six-membered rings because the ring atoms are in general not equivalent and there are more than two different positions that a substituent may occupy. There is in addition the possible existence of pseudorotation as the lowest energy inversion process in any five-membered ring. Thus it is not surprising that only a few such radicals have been studied by EPR. In general, four magnetically equivalent ring β protons are observed in the solution spectra of α-substituted cyclopentyl radicals,[6] implying either that they are inverting rapidly between equivalent nonplanar forms or that they are planar.

One prominent exception is the cyclopentyl radical itself. Line width alternation was some time ago observed in the solution spectrum of this radical, presumably the result of ring

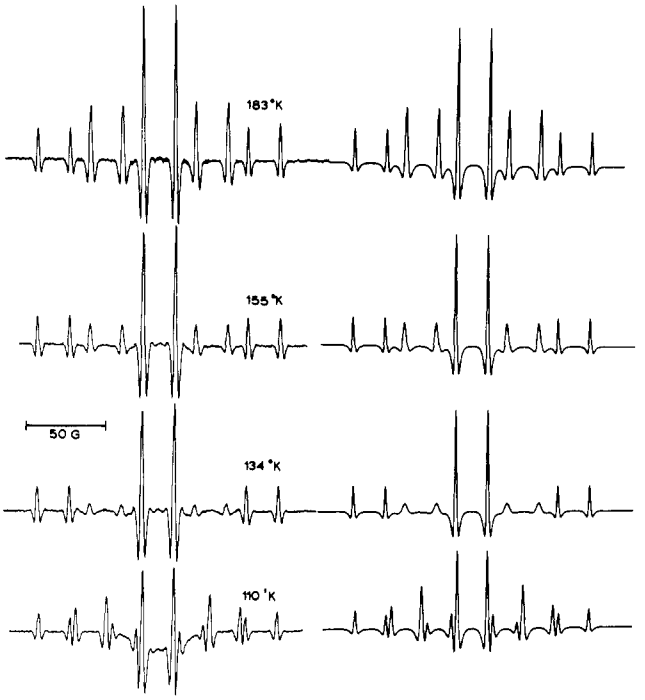


Figure 1. Second-derivative EPR spectra of the cyclopentyl radical in adamantane (left), with computer simulations (right).

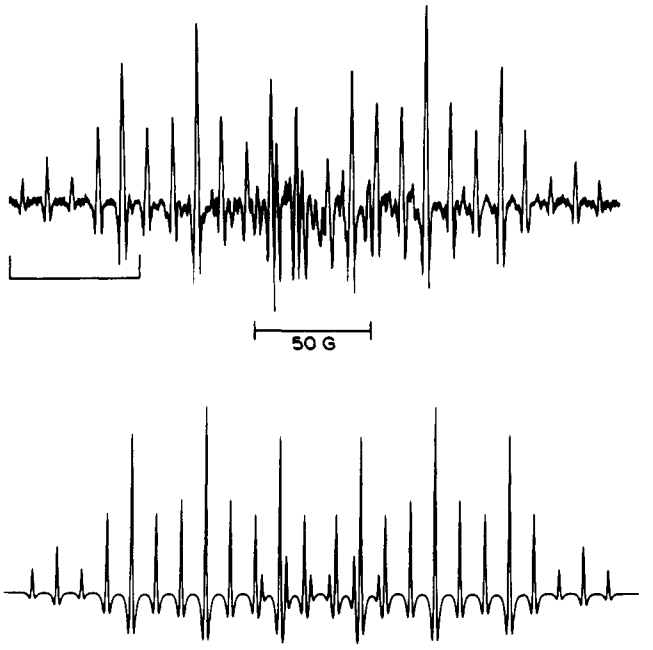
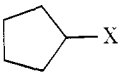


Figure 2. Second-derivative EPR spectrum of the fluoromethylcyclopentyl radical in adamantane-d_{16} at 297 K (top), with a computer simulation (bottom). The lines shown in the bracket are expanded in Figure 3. There are several impurity peaks present in the center of the spectrum.

Table I. EPR Parameters for Substituted Cyclopentyl Radicals



X	Temp, K	a, G[a] H_β ring	H_β CH_2	Other	g[b]
H	110	23.7, 43.3		H_α 20.25	
	215	31.6		H_α 20.25	
CH_3	82	24.0, 41.3	22.6		
	298	32.6	22.6		
$ClCH_2$	241	28.1	5.5	^{35}Cl 19.5	2.0040
FCH_2	297	32.0	11.7	^{19}F 97.1	2.0036
NCO	225	29.8		^{14}N 4.3	

[a] The "best fits" of computed spectra to experimental spectra, ±0.2 G. [b] Relative to DPPH (g = 2.0036), ±0.0002.

inversion.[3b] More recently an activation energy for conformational interchange of 2700 cal/mol was calculated from analysis of variable-temperature EPr spectra in several different matrices.[7,8] Other five-membered ring radicals for which inversion has been observed include those from tetrahydrofuran,[7,8] tetrahydrothiophene,[9] and methyltetrahydrothiophene.[9]

In order to add to the small amount of information available on inversion barriers in five-membered ring radicals and to further study the relation between β substituents and radical geometry,[10] we have obtained and analyzed as a function of temperature the EPR spectra of the cyclopentyl radical and a number of its α-substituted derivatives. We discuss our results below in terms of equilibrium conformations and mechanisms for inversion in these radicals.

II. Experimental Section

Methylcyclopentane (Aldrich) was used as received. Cyclopentanemethyl fluoride was prepared by heating the tosylate of cyclopentanemethanol (Aldrich) with potassium fluoride dihydrate in β,β'-dihydroxydiethyl ether.[10] The 60-MHz ^1H NMR spectrum (T-60) of the redistilled product (bp 47 °C) in parts per million downfield from internal Me_4Si follows: CH_2 (d of d, 3.3, 4.1, J = 6.2, 47.2 Hz), ring m, 1.9. Cyclopentanemethyl chloride was prepared from cyclopentanemethanol and thionyl chloride in pyridine.[11] Cyclopentyl isocyanate was prepared as previously described.[12]

Samples for EPR study were prepared either by recrystallation of purified adamantane from the radical precursor[10] or by cosublimation of the precursor with adamantane-d_{16} (Merck Sharp and Dohme of Canada). The resulting solids were x-irradiated at 77 K or room temperature. EPR spectra were obtained with either Varian V-4502 or Varian E-4 spectrometers, equipped with flow Dewars for variable temperature operation. The scans were calibrated with Fremy's salt (A_N = 13.09 G) and g values were measured relative to DPPH (g = 2.0036). Temperatures were measured by copper-constantan thermocouples permanently inserted into the flow Dewar immediately below the cavities. These were in turn calibrated by replacement of the sample in the cavity with a thermocouple in an identical sample tube.

The resulting spectra were analyzed on the assumption that the observed temperature effects were caused by the interchange of the ring β protons, which were equivalent in two pairs at low temperatures and all four equivalent at high temperatures. Spectra were simulated by means of a computer program that uses the density matrix approach to exchange processes[13] and which requires as input the limiting low-temperature hyperfine splittings (hfs) of the exchanging protons and the rate constant for the exchange. The program was checked with the published data for the hydroxymethyl radical.[13] The rate constant was varied until a satisfactory visual fit between the experimental spectrum and the plotted simulation was obtained. Activation energies for interchange were then obtained from Arrhenius plots of $1/T$ vs. log k.

Spectra could not be obtained below their respective coalescence temperatures for the fluoromethyl-, chloromethyl-, and isocyanatocyclopentyl radicals because of anisotropic line broadening. Therefore, for their simulations it was assumed that the ratio of the two different ring β proton hfs was the same as in the methylcyclopentyl radical.

Since our activation energy for the cyclopentyl radical does not agree with previous results,[7,8] the experimental procedure for this radical will be discussed in greater detail. The sample of cyclopentane in adamantane was x-irradiated at 77 K and annealed to 183 K. Spectra were taken at decreasing temperatures down to 94 K and then at higher temperatures again. The changes with temperature were completely reversible. Below 102 K the radical was frozen in the low-temperature form and it was in the limiting high-temperature form above 216 K.

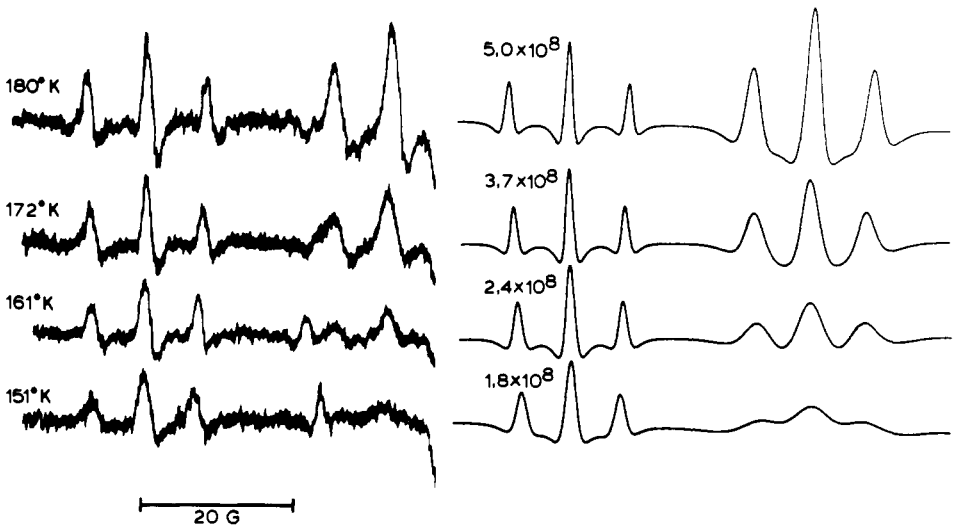


Figure 3. Expanded portion (see Figure 2) of the fluoromethylcyclopentyl radical spectrum as a function of temperature (left), with computer simulations (right). An impurity peak appears at lower temperatures.

III. Results

The EPR spectra observed were in all cases completely consistent with the assumption that the radicals were formed by removal of the tertiary proton from the cyclopentyl ring, as shown below:

The EPR results are listed in Table I and the kinetic parameters E_{act} and A from the Arrhenius equation $\log k = Ae^{-E_{act}/kT}$ are given in Table II. These were determined by least-square fits of the data to straight lines. Typical spectra with computer simulations based on the parameters of Tables I and II are shown in Figures 1-3, and Arrhenius plots of the kinetic data are given in Figures 4 and 5.

Cyclopentyl Radical. Our measured hfs agree well with previous results obtained for the radical in solution[3b] or in the adamantane matrix.[14] The spectrum of the radical in frozen cyclopentane[15] at 77 K was interpreted in terms of inequivalent ring β hfs of 24 and 48 G, and Trofimov and co-workers used 23 and 46 G in their previous studies of cyclopentyl inversion.[7,8] The Arrhenius plot in Figure 5 obviously does not correspond to a single mechanism and the data can be fitted to two straight lines, as shown. Kinetic parameters obtained from both lines are given in Table II.

Methylcyclopentyl Radical. Our EPR data confirm the previously reported results in adamantane.[14] The low-temperature hfs values were measured at 82 K and the high-temperature values at room temperature.

Other Radicals. The fluoromethyl- and chloromethylcyclopentyl radicals are reported for the first time, but the halogen and methylene proton hfs are very similar to those in the corresponding β-halo-*tert*-butyl radicals in adamantane.[10] The large temperature dependences of the fluorine and methylene proton hfs in the two fluoro radicals are almost the same and are plotted for comparison in Figure 6. Likewise the two chloro radicals show a total lack of temperature dependence for the chlorine and methylene proton hfs. The isocyanatocyclopentyl radical was previously studied by us in adamantane at room temperature.[12]

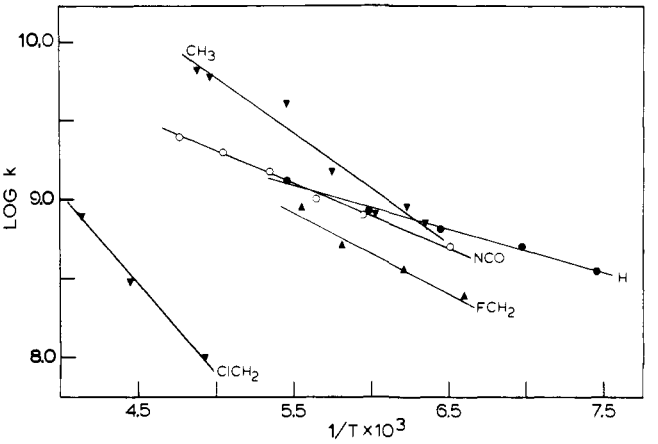


Figure 4. Arrhenius plots of the logarithm of the exchange rate from computer simulations vs. the reciprocal of the absolute temperature for each radical studied with the "best" least-squares straight line drawn through each set of points.

IV. Discussion

The radical site geometry is obviously closely related to the problem of inversion mechanism and several limiting cases can be envisioned that would lead to the observed line width al-

Table II. Kinetic Data for Substituted Cyclopentyl Radicals

X[a]	No. of data points	Temp range, K	E_a,[b] cal/mol	A[b]	Corr coeff.[c]	Radical site geometry
H	3	110-125	2900	12.5	−0.980	
H	5	134-198	1300	10.7	−0.996	Planar
CH_3	6	157-205	3200	13.3	−0.975	Nonplanar
$ClCH_2$	3	203-241	5300	13.6	−0.996	Nonplanar
FCH_2	4	161-180	2400	11.7	−0.979	Nonplanar
NCO	6	153-210	1900	11.4	−0.997	Planar

[a] See heading for Table I. [b] Parameters in the Arrhenius equation, $\log K = Ae^{-E_{act}/kT}$. [c] Least-squares correlation coefficient.

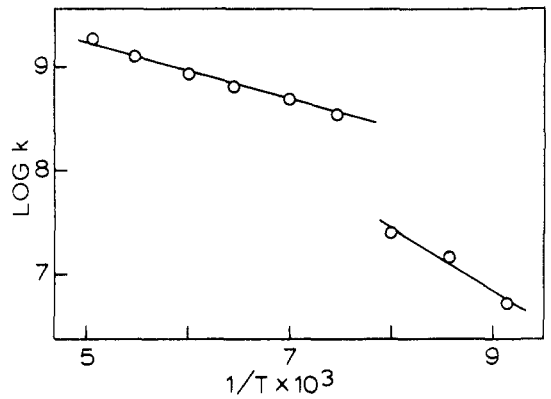


Figure 5. Arrhenius plot (see caption for Figure 4) for the cyclopentyl radical. The higher temperature line is the same as that shown in Figure 4.

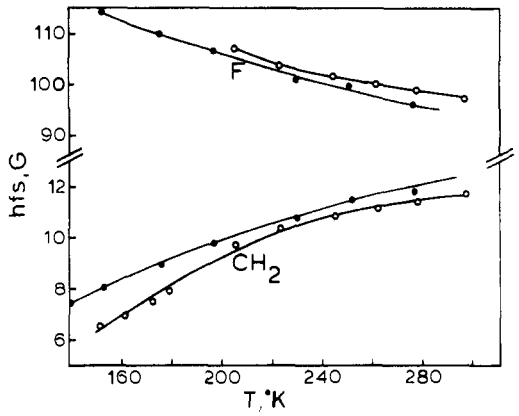


Figure 6. The temperature dependences of the fluorine and methylene proton hyperfine splittings in the fluoro-*tert*-butyl radical from ref 10 (closed circles) and the fluoromethylcyclopentyl radical (open circles). Note the change in the vertical scale.

ternation. First, the results could be caused by inversion at a nonplanar radical site with no contribution by the ring. Second, a radical could invert between two twist forms (T) of the ring, and third, between two envelope forms (E) of the ring, in each case with no change in the radical site conformation. In order to assess the relative contributions of these three cases in each of our radicals, we will first discuss the radical site geometries.

Several of the radicals are almost certainly planar at the trigonal carbon. We have shown previously that the isocyanatocyclopentyl radical is planar,[12] and the cyclopentyl radical by comparison with other secondary alkyl radicals is generally considered to be planar.[16] On the other hand, the *tert*-butyl radical, which is the prototypical tertiary alkyl radical, has been shown by both EPR[17-20] and photoelectron[21] spectroscopy to be nonplanar, and we expect the tertiary alkyl radical studied herein to be nonplanar also.

The two halogenated radicals have, as mentioned above, halogen and methylene proton hfs and temperature dependences almost identical with those of the halogenated *tert*-butyl radicals.[10] For the reasons discussed earlier[22] we conclude that these radicals are nonplanar at the radical site with the C-X bond of the XCH_2^- group eclipsing the unpaired electron orbital, as shown below.

It is apparent that in all of the radicals studied the presence of the ring is important. If it were not, the methylcyclopentyl radical, for example, would be expected to have the same barrier to inversion as the *tert*-butyl radical (500-600 cal/mol[17-20]), but it is actually much larger (Table II). On the other hand, the radical site in particular is involved in at least

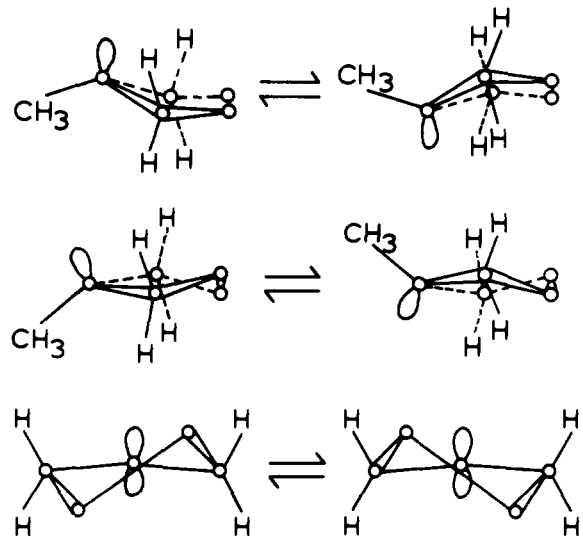
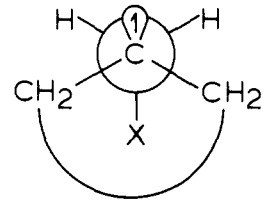


Figure 7. (Top), illustration of the effect of simultaneous radical site and ring inversion with the ring in the E conformation; (middle), the same with the ring in the T conformation; (bottom), inversion of a ring in the T conformation with a planar radical site.



some cases, as shown by the increase in the barrier on going from the fluoromethyl to the chloromethyl radical.

A mechanism for interchange in the nonplanar radicals consistent with the above observations would be radical site inversion accompanied by simultaneous ring inversion (Figure 7, top). The ring inversion must be between the two E conformations, because the ring in the T form would render all four ring β protons magnetically inequivalent (see Figure 7, middle), contrary to the experimental observation that they are equivalent in pairs. For the same reason the $ClCH_2^-$ and FCH_2^- groups must rotate by 180° during the inversion, but this motion would have a very low barrier while the radical site is passing through its planar intermediate stage. Also, if the radical site did not invert, the substituent group would be alternately occupying pseudoaxial and pseudoequatorial positions, which do not have the same energies in substituted cyclopentanes.[23] We did not see any experimental evidence of two forms with different populations.

Radical site inversion obviously cannot be of similar importance in the planar radicals, so that the proton interchange must be caused primarily by inversion of the ring. Both the T and E forms are possible, but because of the similarity of the barriers in the two planar radicals (Table II) in spite of the molecular weight difference of the substituents (H vs. NCO) we suggest that the ring is inverting between equivalent T forms (Figure 7, bottom). This inversion does not involve the radical site while inversion of the E form would require motion of the substituent.

The above discussion applies to the high-temperature data for the cyclopentyl radical (see Figure 5). We cannot comment on the low-temperature data because comparisons with the nonplanar radicals at such low temperatures are not possible. We can only state that a different mechanism of inversion is operative which apparently involves strong interactions with the matrix.

The suggestion that in different cases the two different forms

of the ring are involved is in complete accord with recent ab initio studies of five-membered rings. Cyclopentanone, with a planar trigonal carbon in the ring, is found to have its energy minimum in the T form with interconversion through a planar intermediate,[24] while methylcyclopentane favors the E form with the methyl group occupying the equatorial position.[24]

Our result for the cyclopentyl radical must be compared with the values of 2700–2800 cal/mol reported by Trofimov and co-workers.[7,8] There are not any obvious important differences in experimental procedures and they did not obtain data at sufficiently low temperatures to confirm or deny our observation of a different inversion mechanism. However, the methods of analysis are somewhat different, in that they used a computer program based on a solution of the Bloch equations for the case of two exchanging spins to determine the relative intensities of a broadened and nonbroadened line in the spectrum. We therefore used a similar program to check our results for cyclopentyl and confirmed our original program. Thus we cannot explain the discrepancy except to suggest a systematic error either in programming or in interpretation. The latter might be caused by their large line widths (~25 G).

Finally, we would like to compare our results for radicals with values for inversion barriers in closed-shell compounds. Cyclopentanone has a planar carbon in the ring and is therefore similar to our planar radicals. Both experimental and theoretical results show that the T form is dominant with barriers to planarity of the ring of 2.1 kcal/mol[25] (experimental) and 2.6 kcal/mol[24] (theoretical). Methylenecyclopentane is similarly twisted with a barrier of 1.8 kcal/mol.[25] Therefore, it appears that five-membered rings with a planar trigonal carbon in the ring have barriers for inversion through planar intermediates in the range of 1–2 kcal/mol. On the other hand, substituted cyclopentanes that are nonplanar at the radical site and elsewhere appear to have generally higher barriers that are strongly influenced by the nature of the substituent group. There is no experimental determination of the potential energy surface for methylcyclopentane but the barrier for inversion through a planar intermediate is calculated to be 4.0 kcal/mol.[23]

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Carbon-13 Nuclear Magnetic Resonance Spin–Lattice Relaxation in the *N*-Acylneuraminic Acids. Probes for Internal Dynamics and Conformational Analysis[1a-c]

Michael F. Czarniecki[1d] and Edward R. Thornton*

Contribution from the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104. *Received April 25, 1977*

Abstract: ^{13}C NMR studies of several *N*-acylneuraminic acid derivatives have been made. Spin–lattice relaxation times (NT_1^{DD} = ca. 0.3 s) indicate that the pyranose ring carbons undergo isotropic rotation and that C-7 and C-8, but not C-9, are isotropic with the ring. A model involving an intramolecular hydrogen bond network is supported by the relaxation data. It is shown that calculated values of T_1^{DD} for nonprotonated carbons agree closely with experiment. The isolation of *N*-acetylneuraminic acid from Oriental birds' nest substance is shown to be a convenient source of this compound.

The acyl derivatives of neuraminic acid, the *N*-acetylneuraminic acid having the widest biological distribution, are α ketosidically linked to the glycoproteins and glycolipids of neuronal and other cell membranes.[2] Representing the most complex group of naturally occurring monosaccharides, the neuraminic acid derivatives contain a variety of functionality unusual in carbohydrate chemistry. Moreover, recent evidence has specifically implicated the acylneuraminic acid moieties of glycolipids and glycoproteins in specific mechanisms of cell function, such as intercellular recognition, hormone reception,