# Dynamic NMR as a Nondestructive Method for the Determination of Rates of Dissociation. XIV. Examination of Rates of Proton-Detachment from Ammonium Ions with Multiple Probes[1)]

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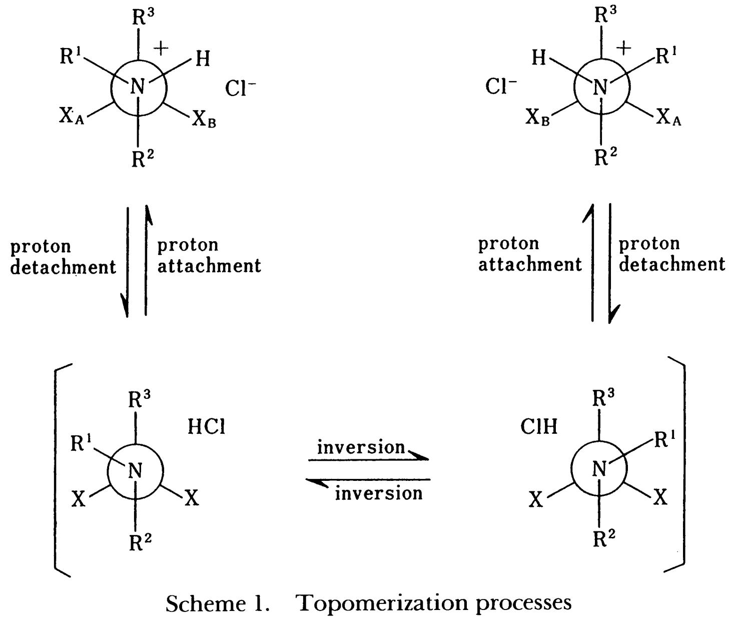
The rates of proton-detachment and those of topomerization in ammonium ions of benzyldiethylammonium chloride and benzylisopropylmethylammonium chloride were determined by dynamic NMR spectroscopy, by taking advantage of loss of coupling of the benzylic methylene or the methyl protons for the former process and site-exchange of the diastereotopic protons at the ethyl-methylene, isopropyl-methyl, or benzylic methylene positions for the latter in $^1$H NMR spectroscopy. The rates of the both processes were in good agreement with each other to indicate that the rate-limiting process in the observed topomerization is the proton-detachment. Thus it is shown that any available probes may be used for the proton-detachment or for the ivestigation of the proton affinity of amines by the dynamic NMR spectroscopy in aprotic solvents. The preference of the probes was discussed.

The knowledge on basicity of amines in aprotic solvents is important in understanding organic reactions, because most of them are carried out in organic solvents and bases are important catalysts in many cases. Although basicity of amines in aqueous solvents has well been documented[2)] and proton affinity of amines in the gas-phase has recently been discussed,[3)] the determination of basicity or proton affinity of amines in organic solvents is not straightforward and lacks general reliability.

In the series of investigation of proton affinity of amines in aprotic solvents by dynamic NMR spectroscopy, we have demonstrated that the dynamic NMR technique is a potentially very useful method in the field of determination of proton affinity of amines in aprotic solvents. In addition to the fact that the proton affinity of the series of *p*-substituted *N*,*N*-dibenzylanilines in chloroform-*d* parallels those of the series of *p*-substituted *N*,*N*-dimethylanilines in water and *p*-substituted anilines in the gas phase,[4)] we have been able to demonstrate that examination of proton affinity of anions derived from strong acids in aprotic solvents is possible by applying the same technique that utilizes a constant amine and a series of acid salts derived therefrom.[5)]

Although this technique is potentially widely applicable, there have remained two points to be clarified before claiming the general applicability. The origin of the problems is that we have used benzylic methylene proton signals, which simultaneously lose coupling and exchange sites on detachment of the proton from the anilinium ion, as a probe in $^1$H NMR spectroscopy.

The topomerization processes involve three steps, as



Scheme 1. Topomerization processes

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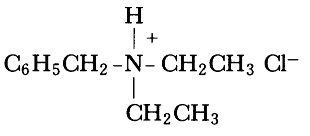
are shown in Scheme 1: proton detachment, inversion of amine, and proton attachment. In the previous work, it was assumed that the rate-limiting step is the proton detachment because the inversion of amine is a rapid process[6] and proton atachment to amine should also be fast. However, this assumption should be confirmed.

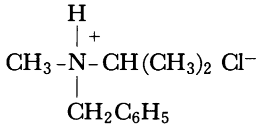
The second problem is that, in the line shape analyses, we have assumed that the coupling constant between the ammonium proton and the benzylic methylene protons in the *N*,*N*-dibenzylanilinium ions is inversely proportional to the rate of proton detachment at a certain range where the rate is reasonably large, since DNMR3 program[7] does not accommodate the two processes involved. This again remains to be confirmed.

To overcome these problems, it is necessary to compare the rates of true proton-detachment with the rates of topomerization which are not affected by the coupling with the detaching proton. After establishing these rates, we may compare the rates of topomerization that are obtained by observing topomerization with concomitant loss of coupling. Thus we designed molecules that conform with these requirements. They are benzyldiethylammonium chloride (**1**) and benzylisopropylmethylammonium chloride (**2**).



$$C_6H_5CH_2\text{-}\underset{\displaystyle CH_2CH_3}{\overset{\displaystyle H}{\overset{|+}{N}}}\text{-}CH_2CH_3\ Cl^-$$

**1**



$$CH_3\text{-}\underset{\displaystyle CH_2C_6H_5}{\overset{\displaystyle H}{\overset{|+}{N}}}\text{-}CH(CH_3)_2\ Cl^-$$

**2**

Compound **1** is an example of aliphatic amines that carry two probes. The benzylic methylene protons should show coupling with the ammonium proton as far as the proton sticks to the amino-nitrogen. This probe should provide the rates of proton-detachment, as has been shown by the case of *N*,*N*-dimethylcyclohexylamine hydrochloride.[8,9] The ethyl-methylene protons are diastereotopic when the proton-detachment is slow and show both site-exchange and loss of coupling with the ammonium proton when the process becomes fast.

Compound **2** provides three probes for the determination of the rates of the observable processes. The coupling of the *N*-methyl protons with the ammonium proton should be lost in the fast exchange limit. The isopropyl-methyls are the probe that should give information of the topomerization but has negligibly small coupling constant with the detaching ammonium proton. Compound **2** also carries benzylic methylene protons that are diastereotopic if the proton detachment is slow, exchange their site on topomerization, and show coupling, that disappears at the fast exchange limit of the ammonium proton, with the ammonium proton at the slow exchange limit. Thus this compound possesses all the necessary probes for comparison of the rate constants.

Syntheses of the compounds in question are straightforward. The hydrochlorides were purified by recrystallization to avoid any complexity arising from the excess of acid or base,[9] and dissolved in 1,1,2,2-tetrachloroethane-$d_2$. The observed and calculated spectra are shown in Figs. 1 and 2, where the line shapes at the same temperature are arranged along the abscissa for the convenience of comparison. The rate constants thus obtained and temperatures were put into the Eyring equation to afford activation parameters which are compiled in Table 1.

As are clear from both figures, the rate constants obtained with the two probes in **1** and those obtained from the three probes in **2** show satisfactory agreement, the disagreement in the rate constants being generally within 10%. The results confirm that the nitrogen-

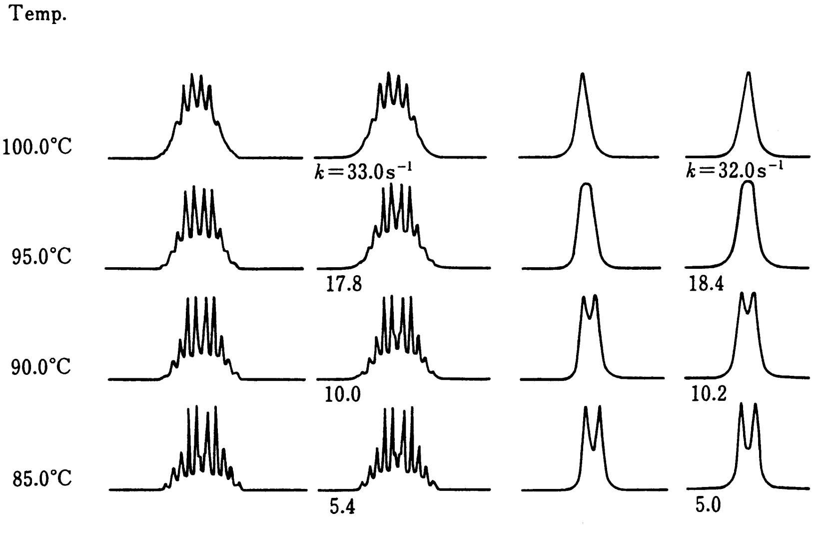


Fig. 1.

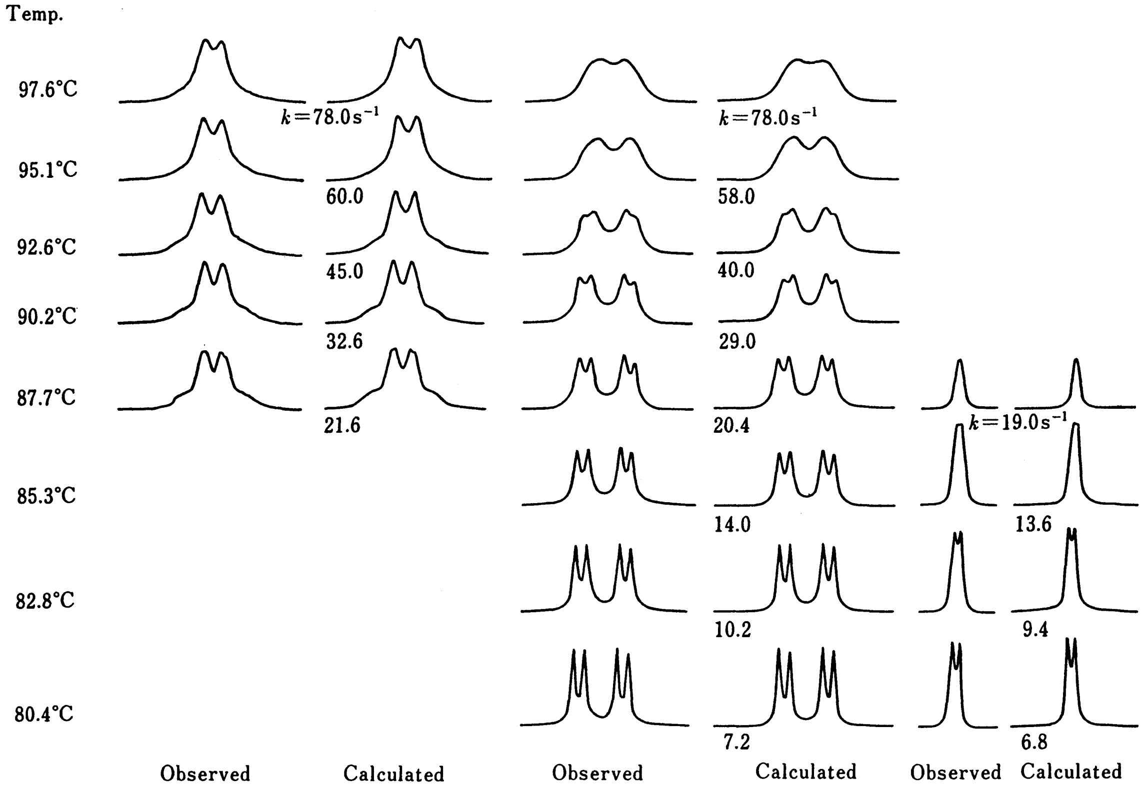


Fig. 2.

Table 1. Activation Parameters for the Rate Processes Observed in Benzyldiethylammonium Chloride (**1**) and Benzylisopropylmethylammonium Chloride (**2**) in $CDCl_2CDCl_2$

| Compound | Probe | $\Delta H^{\neq a)}$ kcal mol$^{-1}$ | $\Delta S^{\neq}$ cal mol$^{-1}$ K$^{-1}$ | $\Delta G^{\neq}_{363}$ kcal mol$^{-1}$ | $r^{b)}$ |
|---|---|---|---|---|---|
| **1** | $CH_3C\underline{H}_2$$^{c)}$ | 31.2±1.8 | 31.5±4.8 | 19.7 | 0.9998 |
| | $C_6H_5C\underline{H}_2$ | 32.0±4.8 | 33.7±13.0 | 19.7 | 0.9988 |
| **2** | $(C\underline{H}_3)_2CH$ | 35.7±0.8 | 46.1±2.1 | 19.0 | 0.9998 |
| | $C\underline{H}_3N$ | 35.2±2.2 | 44.4±6.1 | 19.0 | 0.9998 |
| | $C_6H_5C\underline{H}_2$ | 33.5±5.4 | 40.1±14.7 | 18.9 | 0.9962 |
| | $C_6H_5C\underline{H}_2$$^{c)}$ | 34.6±2.0 | 43.0±5.4 | 19.0 | 0.9992 |

a) 1 cal=4.184 J. b) Correlation coefficient in the statistical treatment. c) Data obtained by decoupling with the ammonium proton.

inversion in these compounds is indeed fast and the rate-limiting step in the topomerization is the proton-detachment, because the proton-attachment to an amine is believed to be diffusion-controlled and is very fast.[10] They also confirm that the probe which shows both site-exchange and the loss of coupling also gives satisfactory results, although the method involves an assumption about the dependence of the coupling constants on the rate of detachment.

The results also suggest that any of the probes available in these amine hydrochlorides may be used in determining the rates of proton-detachment. This finding is quite useful and extends the scope of application of this technique, because an overlap of the line shapes of the exchanging nuclei with other signals often obscures the calculation results, some of the signals due to the exchanging nuclei may be hidden by other signals, or only one type of probes is available in a given molecule. It is now possible to use any of the probes, the loss of coupling, the site-exchange, and the combination of the both phenomena, in determining the proton affinity of amines in aprotic solvents.

A remaining problem is which probe is prefered when multiple of them are available in a given compound. Our choice is the protons of the isopropyl-methyls like in compound **2**. As is clear from Fig. 2, the change in line shapes is observable at the largest range of temperature if the isopropyl-methyl protons are used as probes. The loss of coupling of the methyl protons in **2** is treated as if the chemical shift difference corresponds to the coupling constant.[11] Since usually the coupling constant is small, i.e. ca. 5 Hz for the

CH-NH$^+$ protons, coalescence of the signals takes place in a rather small temperature range. In addition, the determination of the transverse relaxation times ($T_2$) can be problematic in this case because of the simple line shapes as is discussed later. For the diastereotopic proton pair which shows the coupling with the ammonium proton, our approximation forces us to use rather a small temperature range as well. In principle, it is possible to treat the line shapes of this kind of probes by analyzing the loss of coupling first and applying the extrapolated coupling constants to the calculation of the site exchange of the diastereotopic protons, but this procedure is tedious and does not guarantee the reliable data. The discussion presented here favors the use of isopropyl-methyl protons due to the fact that the more rate constants are available than the coupling and coupling-site-exchange cases to make the Eyring plot more reliable.

There is still another point for the preference of the isopropyl-methyl probe. That is, the more complex signals give the more reliable data in the line shape analysis owing to the multitude of checking points in the simulation.[12,13] The simpler line shapes are known to tend to produce large errors especially in entropy of activation. Since coupling with the ammonium proton gives a simple two-singlet pattern, the reliability of the line shape analysis must be considered carefully. The small errors in the activation parameters obtained from the methyl signals in **2** is rather fortuitous, The benzylic methylene signals in **2** should be better than those due to the methyl protons, but the assumption we made seems to deteriorate the quality of the data to some extent.

As the results of these factors, the kinetic parameters obtained from the isopropyl-methyl probes in **2** contain the smallest errors among those obtained here (see Table 1). The errors in the kinetic parameters obtained from the benzylic methylene probe are rather large owing to the approximation we employed. The method cannot avoid the ambiguity in determining the coupling constants and the rate constants (see Experimental part).

Compound **1** casts an additional problem to us. That is, the exchange of the sites of the methylene protons in the ethyl groups is in principle that of $ABL_3X \rightleftarrows BAL_3X$, in addition to the loss of coupling on proton-detachment. This exchange is too complicated for our program. Therefore, we irradiated the the ammonium proton to simplify the exchange to $ABX_3 \rightleftarrows BAX_3$. This operation might cause some error in the line shapes. Since this kind of operation has not been carried out, to our knowledge, in the dynamic NMR study, it was desired to confirm its reliability. If the technique does not involve problems, it will be both convenient and reliable, because the complexity of the signals will guarantee good quality of data.

In order to check the influence on the kinetic parameters given by decoupling operations, we carried out the measurement of the line shapes due to benzylic methylene protons in **2** with irradiation at the ammonium proton frequency. The rate constants were obtained as follows as the results of line shape analysis (rate constants in s$^{-1}$ and temperatures in °C in parentheses are given): 10.0 (82.8), 15.6 (85,3), 20.6 (87.7), 28.8 (90.2), 55.0 (95.1), 76.4 (97.6). Activation parameters derived from these data are given in Table 1 as well. The agreement is excellent with those derived by using other probes and the correlation coefficient satisfactory. The results confirm that the line shape analysis using those produced by decoupling is a satisfactory method.

The feature of the kinetic parameters in Table 1 is very large, positive entropies of activation. The similar values have been obtained for *p*-substituted *N,N*-dibenzylanilinium halides[4,5] and for [*o*-(diethylaminomethyl)phenyl]halodimethylstannanes.[14] Large, positive entropies of activation seem to be general in the process when one goes from the ionic ground state to the less ionic transition state, The freedom of motion of solvent molecules must increase in the transition state in these cases.

Close examination of the data in Table 1 reveals that compound **2** gives a larger entropy of activation than **1** which in turn gives a larger entropy of activation than the *N,N*-dibenzylanilinium chloride (18—24 cal mol$^{-1}$ K$^{-1}$).[4] This will probably mean that the transition state for the proton-detachment in an ammonium ion derived from a strong base is later than in that derived from a weak base. The apparent trend we have seen in the series of *N,N*-dibenzylanilinium chlorides, namely the trend that a weak base gives a larger entropy of activation for the proton-detachment than a strong,[4] is now concluded not significant. The fortuitous trend was caused by the errors involved in the line shape analysis of the benzylic methylene proton signals which simultaneously lose coupling and exchange sites on proton-detachment.

## Experimental

**Materials.** *N,N*-Diethylbenzylamine, bp 60—62 °C/3.5 mmHg (1 mmHg=133.322 Pa) (lit,[15] bp 211—212 °C), was prepared by a standard method starting from benzyl chloride and diethylamine. $^1$H NMR (CDCl$_3$) $\delta$=1.01 (6H, t, $J$=7.0 Hz), 2.49 (4H, q, $J$=7.0 Hz), 7.1—7.4 (5H, m). *N*-Isopropyl-*N*-methylbenzylamine, bp 60—62 °C/3.5 mmHg, was prepared by formylation of *N*-isopropylbenzylamine by a standard method and by reduction of the resulting formyl compound with lithium tetrahydridoaluminate. $^1$H NMR (CDCl$_3$) $\delta$=1.07 (6H, d, $J$=7.0 Hz), 2.13 (3H, s), 2.86 (1H, sept, $J$=7.0 Hz), 3.84 (2H, s), 7.2—7.4 (5H, m).

The hydrochlorides of the amines were prepared by dissolving them in hexane and introducing hydrogen chloride gas into the solution. The precipitates thus obtained were recrystallized from tetrahydrofuran.

**Benzyldiethylammonium Chloride (1),** mp 182—183 °C. Found: C, 66.22; H, 8.97; N, 7.05; Cl, 17.80%, Calcd for

$C_{11}H_{18}ClN$: C, 66.15; H, 9.08; N, 7.01; Cl, 17.75%. $^1H$ NMR ($CDCl_3$) $\delta=1.46$ (6H, t, $J=7.3$ Hz), 3.07 (4H, m), 4.16 (2H, d, $J=5.3$ Hz), 7.4—7.7 (5H, m), 12.43 (1H, br s).

**Benzylisopropylmethylammonium Chloride (2),** mp 126—127 °C. Found: C, 66.01; H, 9.02; N, 7.10; Cl, 17.65%. Calcd for $C_{11}H_{18}ClN$: C, 66.15; H, 9.08; N, 7.01; Cl, 17.75%. $^1H$ NMR ($CDCl_3$) $\delta=1.36$ (3H, d, $J=6.4$ Hz), 1.52 (3H, d, $J=6.4$ Hz), 2.63 (3H, d, $J=4.8$ Hz), 3.49 (1H, m), 4.15 (2H, m), 7.4—7.8 (5H, m), 12.27 (1H, br s).

**Dynamic NMR Spectral Study.** The spectral measurement was carried out with either a JEOL FX-200 or JEOL GX-270 spectrometer. Since we used a spectrometer that operated at 60 MHz for the determination of rates of proton-detachment in *N,N*-dibenzylanilinium halides,[4,5] the 200 MHz machine was more convenient for comparison due to the fact that the 270 MHz machine gave apparently different line shapes because of the larger chemical shift differences. Samples were dissolved in 1,1,2,2-tetrachloroethane-$d_2$, which was dried over Molecular Sieves 4A, to make up ca. 50 mmol $L^{-1}$ solutions.

Temperature was determined by a thermocouple. The chemical shift differences of the exchanging nuclei and coupling constants were checked at the slow exchange limits. All the coupling constants were found to be temperature-independent, whereas the chemical shift differences changed linearly with the temperature. The chemical shift differences were at least checked at four temperatures to find that they were linearly correlated with temperature, except for the isopropyl-methyl proton signals, of which chemical shift differences were temperature-independent. The results are shown in Table 2. These straight lines were extrapolated to the temperatures where the change in line shapes was observed. The simulation was carried out with the use of DNMR3 program.[7] $T_2$ was estimated from the line width due to the undeuterated solvent molecules and was adjusted to give the best fit in simulation for the line shapes involved in the site-exchange. Thanks to the complexity of the signals, changes in $T_2$ and rate constant $k$ gave different effects on the line shapes in these cases, as were observed in other complex signals,[16] thus enabling us to determine $T_2$ and $k$ uniquely.

For the simulation of the exchanging benzylic methylene proton signals, $ABX \rightleftharpoons BAX$, that lose coupling on dissociation of the ammonium proton was performed in the following way. At the coalescence temperature where the quadruplet-doublet became a broad quadruplet, the rate constant of the proton-detachment and the $J_{AX}$ and $J_{BX}$ values, the rough values of which were estimated from those at low temperatures, were used as variants and the $T_2$ and the chemical shift differences between A and B, which could be derived as above, were taken as given. The best fit values of the rate constant and the coupling constants were sought in the simulation of the line shapes. After determining the rate constant at the temperature, then the coupling constants, $J_{AX}$ and $J_{BX}$, were treated as inversely proportional to the rate constant of proton-detachment. The obtained rate constants were doubled for comparison with the data obtained from the loss of coupling because the topomerization takes place only when the proton attaches to the amine after inversion of the amine and the attachment at the same configuration is not counted in the topomerization.

Table 2. Equations Correlating the Chemical Shift Differences and Temperature in Given Probes in **1** and **2**

| Compound | Probe | $f(T)$[a] | External magnetic field |
|---|---|---|---|
| | | | MHz |
| **1** | $CH_3C\underline{H}_2$ | $42.9-0.040T$ | 270 |
| | $(C\underline{H}_3)_2CH$ | $26.5\pm0.000T$ | 200 |
| **2** | $C_6H_5C\underline{H}_2$ | $-63.8+0.235T$ | 200 |
| | $C_6H_5C\underline{H}_2$[b] | $-85.2+0.313T$ | 270 |

a) $f(T)$ for $\Delta\nu/\mathrm{Hz}=f(T)/\mathrm{K}$. b) Decoupled with the ammonium proton.

For the simulation of the line shapes which change owing to the detachment of the ammonium proton, the principle established for methylamine in dilute hydrochloric acid[11] was used. The spin-spin coupling constants were invariant within the slow exchange limit. $T_2$ was estimated from the line width of the undeuterated solvent peak and this value was used throughout the simulations of the spectra at various temperatures. Since the changes in $k$ and $T_2$ gave similar trends in the modification of the line shapes, there remains ambiguity in the rate constants thus obtained to some extent.

For the decoupled measurements, care was exercised for not affecting the line shapes in the slow exchange limit. The irradiation of the ammonium proton was carried out at the center of the broad signal. The irradiation power was IRATN 130.

The measurement of the $^1H$ NMR spectra at 200 MHz was carried out at Showa Denko Company, Ltd. We wish to thank for the permission of the use of the instrument. The work was supported by a Grant-in-Aid (No. 61134043) for Fundamental Scientific Research of the Ministry of Education, Science and Culture.

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